

Exhibit 1

Stephen S. Hecht, Ph.D.

Winston R. and Maxine H. Wallin Land Grant Professor of Cancer Prevention
American Cancer Society Professor, American Chemical Society Fellow
Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55455

Education

Duke University, B.S. (with honors), Chemistry – 1964
Massachusetts Institute of Technology, Ph.D., Organic Chemistry – 1968

Professional Experience

Masonic Cancer Center, University of Minnesota, Minneapolis, MN

- Wallin Land Grant Professor of Cancer Prevention and Professor, Department of Laboratory Medicine and Pathology, 1996-present
- Head, Carcinogenesis and Chemoprevention Program, 1998-2014
- Member, Medicinal Chemistry and Pharmacology Graduate Programs, 1996-present

American Health Foundation, Valhalla, NY

- Director of Research, 1987-1996
- Chief, Division of Chemical Carcinogenesis, 1980-1996
- Head, Section of Organic Chemistry, Division of Environmental Carcinogenesis, 1973-1980

United States Department of Agriculture, Philadelphia, PA

- National Research Council Fellow, 1971-1973

Haverford College, Haverford, PA

- Assistant Professor of Chemistry, 1969-1971

Massachusetts Institute of Technology, Cambridge, MA

- Postdoctoral Fellow, Mass Spectrometry, Professor Klaus Biemann, 1968-1969

Honors and Awards

Academy for Excellence in Team Science, University of Minnesota, 2019

Listed in AACR Landmarks in Cancer Research, 2017: Tobacco-Specific Nitrosamines, *JNCI* 60: 819-824 (1978)

University of Minnesota Medical School Dean's Distinguished Research Lectureship, 2017

American Chemical Society Minnesota Section, Minnesota Award, 2017

University of Minnesota Medical School Wall of Scholarship, 2015

Elected American Association for the Advancement of Science Fellow, 2014

Selected as next Editor-In-Chief, *Chemical Research in Toxicology*, American Chemical Society, 2012

Joseph Cullen Award, American Society of Preventive Oncology, 2012

Elected American Chemical Society Fellow, 2009

Founders' Award, Division of Chemical Toxicology, American Chemical Society, 2009

Academy for Excellence in Health Research, Academic Health Center, University of Minnesota, 2006

American Association for Cancer Research-Cancer Research and Prevention Foundation Award for Excellence in Cancer Prevention Research, 2006

Merit Award, National Cancer Institute, 2004-2014

Dr. William Cahan Distinguished Professor Award, Flight Attendant Medical Research Institute, 2002

Alton Ochsner Award Relating Smoking and Health, 2001

American Cancer Society Research Professor, 2000-2009

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Hecht

Wallin Chair in Cancer Prevention, Masonic Cancer Center, University of Minnesota, 1996-
Endowed Chair in Carcinogenesis and Chemoprevention, American Health Foundation, 1992-1996
Cancer Research Covers: March 1, 1988; February 15, 1993
Chemical Research in Toxicology Covers: June 1998, July 2007, February 2011
Cancer Epidemiology Biomarkers & Prevention Cover, December 2003
Outstanding Investigator Grant, National Cancer Institute, 1987-2001
Research Career Development Award, National Cancer Institute, 1975-1980
National Research Council Fellow, 1971-1973
Phi Beta Kappa, 1964

Current Research Interests

- Mechanisms and prevention of cancer induced by tobacco products and environmental agents
- Carcinogen biomarkers and their application in molecular epidemiology and cancer prevention
- Mechanisms of chemical carcinogenesis in humans
- Prevention of environmental carcinogenesis by naturally occurring agents

Selected Active Grant Support

Principal Investigator

Continually funded by the U.S. National Cancer Institute since 1975

- NCI, CA-81301, Metabolism of Carcinogenic Tobacco-Specific Nitrosamines, 1999-
- NCI, CA-203851, e-Cigarettes: Formaldehyde DNA Adducts, Oxidative Damage, and Potential Toxicity and Carcinogenesis, 2017-
- NCI, CA-222005, Clinical Trial of Watercress in Detoxification of Environmental Toxicants and Carcinogens, 2018 –
- NCI, CA-263084, High Resolution Mass Spectrometric Profile Analysis of Carcinogen-DNA Adducts in Oral Cells of Cigarette Smokers and Squamous Cell Carcinoma of the Head and Neck, 2021-
- NCI, CA-138338 (P01), Mechanisms of Ethnic/Racial Differences in Lung Cancer due to Cigarette Smoking, 2010 -

Co-Investigator

NIEHS, Minnesota HHEAR Exposure Assessment Hub

Selected Professional Activities

Peer Review

Special Emphasis Panel, NCI PREVENT Cancer Program, 2011 –
AACR-Johnson & Johnson Lung Cancer Innovation Science Grants Committee, 2017-
NIH Center for Scientific Review Special Emphasis Panel, Member 2020; Chair, 2019
NIH Cancer Prevention Study Section, ad hoc, 2018
NIEHS Childrens' Health Exposure Analysis Resource Access Committee, 2017
Special Emphasis Panel, NCI SPORE grants, 2015
Council for Extramural Grants, American Cancer Society, 2010-2014
Chair, Chemo/Dietary Prevention Study Section, National Institutes of Health 2006-2009
Board of Scientific Counselors, Subcommittee 2, Basic Sciences, National Cancer Institute, 2001-2004
Peer Review Committee on Carcinogenesis, Nutrition, and the Environment, American Cancer Society, 1998-2001; Chair, 2001
Grants Review Panel, American Institute for Cancer Research, 1984-1987
Chemical Pathology Study Section, National Institutes of Health, 1981-1985

Ad Hoc Reviewer:

National Cancer Institute, Cancer Center Support Grant Program
National Institute of Environmental Health Sciences
Dutch Cancer Society
Florida Department of Health
Alberta Heritage Foundation for Medical Research
Veterans Administration
New Jersey Commission on Cancer Research
United States - Israel Bi-national Science Foundation
California Tobacco Related Disease Research Program
Ohio Cancer Research Associates

Selected Advisory Groups and Related Activities

World Health Organization, TobReg Committee New Nicotine Products, Tbilisi, Georgia, ad hoc, 2022
AACR Cancer Prevention Working Group, 2021-
European Food Safety Authority, Contamination Working Group on N-Nitrosamines in Food, 2020-2023
National Research Council Committee on Health Effects and Patterns of Use of Premium Cigars, 2020-2022
U.S. Food and Drug Administration Panel on N-Nitrosamines in Pharmaceutical Products, 2021
Panel Member, 2018 American Cancer Society Professors' Meeting Discussion: "Bad luck" hypothesis
Member (ad hoc), Tobacco Products Scientific Advisory Committee, FDA, 2018-
Reviewer, U.S. National Academies, Public Health Risks and Benefits of e-Cigarettes, 2017
Nomination Committee, Division of Chemical Toxicology, American Chemical Society, 2017-2019; Awards
Committee, 2019-2021, Chair 2021
Expert Consultation on the Integrated Exposure-Response Function, Univ. of Washington, 2017
Data Safety and Monitoring Board: NHLBI HAPIN study, Household Air Pollution and Health, 2017-
Chair, Nominating Committee, American Chemical Society Sosnovsky Award for Cancer Research, 2014
International Agency for Research on Cancer Monographs Program, Peer Review Committee, 2014
Frontiers in Cancer Prevention Annual Meeting, Program Committee, 2013
Round Table Meeting of the Senate Commission on Food Safety of the German Research Foundation: Nitrate and
Nitrite in the Diet, Bonn, Germany, 2012
International Agency for Research on Cancer, Workshops on Tumor Concordance and Meshansims of
Carcinogenesis, Lyon, France, 2012
Institute of Medicine, Committee on Scientific Standards for Studies on Reduced Risk Tobacco Products, 2011
AACR Cancer Prevention Committee and Cancer Prevention Summit, 2016
Tobacco Constituents Subcommittee, TPSAC, U.S. Food and Drug Administration, 2010
Flavor and Extract Manufacturers Association Expert Panel, 2010-
AACR Task Force on Tobacco and Cancer, 2009- 2012
External Advisory Board, University of Illinois Cancer Center, 2010-2014
Advisory Committee, Translational Cancer Research Center, South Dakota State University, 2009-2014
Chair-Elect to Past Chair, Chemistry in Cancer Research Working Group, AACR, 2007-2009
Chair, Program Committee, AACR Conference, Chemistry in Cancer Research: A Vital Partnership, 2007
Member, NCI-SRNT FDA Tobacco Regulation Legislation Review Project, 2009
International Agency for Research on Cancer, Knowledge Synthesis in Gene-Environment Interactions in
Cancer, Lyon, France, 2009
Strategic Dialogue on Tobacco Harm Reduction, 2006-2007
Committee on Defining Upper Limits for Tobacco Toxicants, WHO TobReg, 2006-2007
Chair, Scientific Advisory Board, Center for Excellence in Environmental Toxicology, University of Pennsylvania,
2005-2010
Chemistry in Cancer Research, AACR, Think Tank of Leaders in the Field, 2005

Chapter Editor for Cancer, Surgeon General's Report, How Cigarette Smoking Causes Disease, 2010
Contributor, Surgeon General's Report, Passive Smoking and Health, 2004; Health Consequences of Smoking, Fifty Years of Progress, 2014
Co-organizer, Symposium on Tobacco Carcinogenesis, American Chemical Society National Meeting, 2005
Program Committee Co-Chairperson, AACR Frontiers in Cancer Prevention Meeting, 2004, 2007
National Cancer Institute Carcinogenesis Think Tank, 2004
National Cancer Institute Biotechnology Initiative for Cancer Public Health Working Group, 2004
National Tobacco Monitoring, Research, and Evaluation Workshop, 2002
International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 37, *Tobacco Habits Other than Smoking*, 1985; Vol. 83, *Tobacco Smoke and Involuntary Smoking*, 2002; Vol. 85, *Betel Quid and Areca Nut*, Chair, 2003; Vol. 89, *Smokeless Tobacco and Some Related Nitrosamines*, 2004; Vol 100E, *A Review of Human Carcinogens-Lifestyle Factors*, 2009
International Agency for Research on Cancer Handbooks on Cancer Prevention, Vol. 9, *Cruciferous Vegetables, Isothiocyanates, and Indole-3-carbinol*, 2003
Lung Cancer Progress Review Group, Co-Chair, Chemoprevention Section, National Cancer Institute, 2001
Board of Scientific Counselors, National Toxicology Program, 1997-2001
Science Advisory Board, National Center for Toxicological Research, FDA, 1998-2002
Board of Scientific Counselors, Division of Cancer Etiology, National Cancer Institute, 1989-1995
Division of Chemical Toxicology, American Chemical Society, Chair, 1999-2000; Chair-elect, 1997-1998; Program Chair, 1996; Chair, Nominations Committee, 2011
Board of Directors, Minnesota Smoke Free Coalition, 1997-2001
Health Research Committee, Health Effects Institute, 1992-1996
External Scientific Advisory Board, Ohio State University Comprehensive Cancer Center, 2002-2006
Corporation Visiting Committee, Division of Bioengineering and Environmental Health, Massachusetts Institute of Technology, 2000-2003
External Advisory Committee, Environmental Health Sciences Center, Oregon State University, 1996-2000
Cancer Prevention Think Tank, American Cancer Society, 1995
American Association for Cancer Research Program Committee, 1983, 1990, 1993, 1997, 1999, 2000, 2003-2005, 2009 (co-chair), 2010; Session Chair, 1984, 1986, 1988, 1991, 200, 2003
Advisory Group, Center in Molecular Toxicology, Vanderbilt University School of Medicine, 1991-1997; Chair, 1995-1997
Advisory Panel, Inhalation Toxicology Research Institute, 1990-1996
Advisory Panels, Chemical Industry Institute of Toxicology, 1990-1996
Advisory Panel, NYU-Nelson Institute of Environmental Medicine, 1992-1995
Peer Review Committee-Scientific Council, International Agency for Research on Cancer, 1991
Upper Aerodigestive Cancer Working Group, National Cancer Institute, 1986-1989
Contributor, Surgeon General's Report on the Health Consequences of Using Smokeless Tobacco, 1986

Editorial Activities

Editor-in-Chief, *Chemical Research in Toxicology*, 2013 - 2017
Associate Editor, *Journal of Medicinal Chemistry*, 2004 - 2012
Associate Editor, *Nicotine and Tobacco Research*, 2009 - present

Editorial Boards:

Cancer Epidemiology, Biomarkers, and Prevention, 1990 - present
Cancer Prevention Research, 2008 – present
Mutagenesis, 2014 - present
Toxics, 2022 - present
Molecular Cancer Therapeutics, 2001 - 2012

Cancer Research, 1980 - 2000; 2010 - 2012
Journal of Environmental Science and Health, Part C, 2016 - present
Chemical Research in Toxicology, 1988 - 1990, 1992 - 1994, 2010 - 2012
Lung Cancer, 2001 - 2012
Cancer Letters, 1999 - 2006
Carcinogenesis, 1986 - 1990; 2001 - 2006
Chemico-Biological Interactions, 1992 - 1998
Mutation Research, 2002 - 2007
Clinical Cancer Research, 2007 - 2011

Selected Invited Lectures and Conferences, 2002-2022

Cancer Research Campaign, Manchester, England	Biomarkers
State University of New York, Stony Brook	Roswell Park Cancer Center
Society of Toxicology National Meetings	Hanna Symposium, Univ. of Minnesota
New York University	New Jersey Governor's Conference on Cancer
Virginia Piper Cancer Research Institute	Prevention
Vanderbilt University	American Chemical Society National Meetings
Reducing Tobacco Harm Conference, Washington, DC	Dietary Factors and Cancer Prevention, Rochester, MN
Diet and Optimum Health, Portland, OR	Wadsworth Center, Albany, NY
American Cancer Society, Atlanta, GA	University of Pennsylvania
Mechanisms of Carcinogenesis and Xenobiotic	University of Iowa
Metabolism, Rutgers University	University of Louisville
International Symposium on Polycyclic Aromatic	University of Kentucky
Compounds	3M Company, St. Paul, MN
EMS Special Conference, Breast Cancer and	Reducing Tobacco Use in Minnesota
Environmental Mutagens	Penn State, Hershey Medical Center
Mayo Clinic, Rochester, MN	Northwestern University
Biomarkers for Tobacco Exposure, Minneapolis	MD Anderson Cancer Center (2)
University of Wisconsin	University of Utah
Ohio State University	Abbott Laboratories
National Cancer Institute Chemoprevention Branch	Virginia Commonwealth University
Columbia University	Medical University of South Carolina
Society for Research on Nicotine and Tobacco	Environmental Mutagen Society, Puerto Rico
East-West Conference on Tobacco and Alcohol	Dartmouth University
Tobacco Harm Reduction Network	Toxicology Forum, Washington, DC
Chemistry in Cancer Research	Tulane University
National Cancer Institute – Frederick	Indiana University
Evaluation of Smokeless Tobacco, Washington, DC	South Dakota State University
University of California, San Diego	EOHSI, Rutgers University/UMDNJ
AACR Frontiers in Cancer Prevention Meetings	World Conference on Tobacco or Health, Mumbai
AACR National Meetings	International Agency for Research on Cancer, Lyon
Society for Research on Nicotine and Tobacco	Ohio State University
University of North Carolina	University of Arizona Cancer Center
Hormel Institute	University of Oklahoma
University of Pittsburgh	UCLA Molecular Toxicology
National Cancer Institute – Causes of Cancer	University of Tennessee
National Cancer Institute – Methods and	Microsomes and Drug Oxidation, Beijing

University of Sao Paulo, Brazil
ETH, Zurich
Biomarkers Workshop, Münster, Germany
Medical College of Wisconsin
Healthy Foods, Healthy Lives Symposium, Univ. of
Minnesota
Japan Society of Clinical Oncology, Yokohama
Nitrate and Nitrosamines, Bonn, Germany
Gordon Research Conference Drug Metabolism,
Keynote Speaker
Brown University
University of Rhode Island
Minnesota Department of Health
Beijing University of Technology
Peking University
National Center for Nanoscience and Technology,

Beijing
U.S. Food and Drug Administration-e-Cigarettes
North Dakota State University
U.S. Food and Drug Administration-Biomarkers
Joint AACR/IASLC Meeting, San Diego
ETH, Zurich
IASLC Meeting, Vienna, Austria
University of Pittsburgh
Penn State Cancer Institute
King's College, London
American Association for Dental Research
Minnesota Department of Health
Kaohsiung Medical University, Taiwan
University of Florida

University Activities

Principal Lecturer and Organizer

Chemical Carcinogenesis and Chemoprevention, 3 credits, 1998 - 2003

Lecturer

Chemical Aspects of Drug Metabolism and Bioactivation
Advanced Pharmacology
Cancer Epidemiology
Molecular Epidemiology

Academic Program Memberships

Medicinal Chemistry Graduate Program
Pharmacology Graduate Program
Combined M.D./Ph.D. Program

Committees

Masonic Cancer Center: Executive Committee and Cancer Prevention and Control Steering Committee,
1998-2014
Masonic Cancer Center Space Committee, 2016 -
M.D./Ph.D. Program Steering Committee, 2000 - 2009

Memberships

American Association for Cancer Research
American Association for the Advancement of Science
American Chemical Society
American Society for Mass Spectrometry
International Society for the Study of Xenobiotics
Society for Research on Nicotine and Tobacco

Selected Contributions to Science (with key references)

1. *Tobacco-specific nitrosamines: identification in tobacco products, carcinogenicity, metabolism, DNA binding, and biomarkers.* The tobacco-specific nitrosamines *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are considered to be important causes of tobacco-induced cancer. We carried out most of the carcinogenicity, metabolism, and DNA binding studies of NNN and NNK, leading to a broad understanding of their uptake and metabolism in humans. We developed highly sensitive mass spectrometric methods for analysis of their metabolites in humans; the NNAL biomarker in particular has been widely used in multiple studies of tobacco-specific carcinogen exposure and risk for cancer. Our studies on NNAL in the urine of non-smokers exposed to secondhand smoke contributed to the clean indoor air now enjoyed nearly universally.
 - a. **Hecht, S. S.**, Carmella, S. G., Murphy, S. E., Akerkar, S., Brunnemann, K. D., and Hoffmann, D. (1993) A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *N. Engl. J. Med.* 329, 1543-1546.
 - b. **Hecht, S. S.** (1998) Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem. Res. Toxicol.* 11, 559-603.
 - c. **Hecht, S. S.**, Stepanov, I., and Carmella, S. G. (2016) Exposure and metabolic activation biomarkers of carcinogenic tobacco-specific nitrosamines. *Acc. Chem. Res.* 49, 106-114. PMID: PMC5154679
 - d. Li, Y., and **Hecht, S. S.** (2021) Identification of an *N'*-nitrosonornicotine-specific deoxyadenosine adduct in rat liver and lung DNA. *Chem. Res. Toxicol.* 34, 992-1003.
2. *Application of tobacco carcinogen and toxicant biomarkers in clinical and epidemiologic studies.* We developed a panel of urinary tobacco carcinogen and toxicant biomarkers, using state of the art high throughput liquid chromatography-mass spectrometric techniques, and have applied these methods in collaborative studies to explore human exposure and risk. Using samples from nested case-control studies within prospective cohorts, we demonstrated that NNAL, nicotine metabolites, and phenanthrene tetraol (a PAH metabolite) were significantly related to lung cancer and that NNN was significantly related to esophageal cancer. We further showed significant differences in levels of these metabolites in ethnic groups with differing risks for lung cancer, and have analyzed more than 60,000 urine samples for multiple biomarkers in a clinical study of the reduced nicotine cigarette.
 - a. Yuan, J. M., Knezevich, A. D., Wang, R., Gao, Y. T., **Hecht, S. S.**, and Stepanov, I. (2011) Urinary levels of the tobacco-specific carcinogen *N'*-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers. *Carcinogenesis* 32, 1366-1371. PMID: PMC3202311
 - b. Park, S. L., Carmella, S. G., Ming, X., Stram, D. O., Le Marchand, L., and **Hecht, S. S.** (2015) Variation in levels of the lung carcinogen NNAL and its glucuronides in the urine of cigarette smokers from five ethnic groups with differing risks for lung cancer. *Cancer Epidemiol. Biomarkers Prev.* 24, 561-569. PMID: PMC4355389
 - c. Yuan, J. M., Nelson, H. H., Carmella, S. G., Wang, R., Kuriger-Laber, J., Jin, A., Adams-Haduch, J., **Hecht, S. S.**, Koh, W. P., and Murphy, S. E. (2017) *CYP2A6* genetic polymorphisms and biomarkers of tobacco smoke constituents in relation to risk of lung cancer in the Singapore Chinese Health Study. *Carcinogenesis* 38, 411-418. PMID: PMC6248819
 - d. Hatsukami, D. K., Luo, X., Jensen, J. A., al'Absi, M., Allen, S. S., Carmella, S. G., Chen, M., Cinciripini, P. M., Denlinger-Apte, R., Drobos, D. J., Koopmeiners, J. S., Lane, T., Le, C. T., Leischow, S., Luo, K., McClernon, F. J., Murphy, S. E., Paiano, V., Robinson, J. D., Severson, H., Sipe, C., Strasser, A. A., Strayer, L. G., Tang, M. K., Vandrey, R., **Hecht, S. S.**, Benowitz, N. L., and Donny, E. C. (2018) Effect of

immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. *JAMA* 320, 880-891. PMID: PMC6372240

3. *Metabolism and DNA adducts of PAH and aldehydes.* We carried out extensive studies on metabolism and DNA adduct formation by these compounds. The results of these studies were consistent with, expanded, and supported the bay region diol epoxide model of PAH carcinogenicity, leading us to develop the phenanthrene tetraol biomarker of PAH exposure plus metabolic activation, and to use high resolution mass spectrometry for analysis of benzo[a]pyrene-DNA adducts in the human lung. Our studies on nitrosamine metabolism evolved to investigations of related metabolically formed aldehydes. Our group was the first to identify acrolein and crotonaldehyde-derived DNA adducts that have been extensively investigated, and we developed the first methods for reliable quantitation of formaldehyde and acetaldehyde-DNA adducts in humans. The latter are particularly relevant to alcohol consumption and its role in carcinogenesis.
 - a. Balbo, S., Meng, L., Bliss, R. L., Jensen, J. A., Hatsukami, D. K., and **Hecht, S. S.** (2012) Kinetics of DNA adduct formation in the oral cavity after drinking alcohol. *Cancer Epidemiol. Biomarkers Prev.* 21, 601-608. PMID: PMC3319307
 - b. Villalta, P. W., Hochalter, J. B., and **Hecht, S. S.** (2017) Ultrasensitive high-resolution mass spectrometric analysis of a DNA adduct of the carcinogen benzo[a]pyrene in human lung. *Anal. Chem.* 89, 12735-12742. PMID: PMC6027747.
 - c. Yang, J., Balbo, S., Villalta, P. W., and **Hecht, S. S.** (2019) Analysis of acrolein-derived 1,N²-propanodeoxyguanosine adducts in human lung DNA from smokers and nonsmokers. *Chem. Res. Toxicol.* 32, 318-325. PMID: PMC6644703
 - d. Chen, M., Carmella, S. G., Li, Y., Zhao, Y., and **Hecht, S. S.** (2020) Resolution and quantitation of mercapturic acids derived from crotonaldehyde, methacrolein, and methyl vinyl ketone in the urine of smokers and nonsmokers. *Chem. Res. Toxicol.* 33, 669-677. PMID: PMC7193944
4. *Chemoprevention of cancer.* We applied our understanding of mechanisms of tobacco carcinogenesis to the identification of potential naturally occurring agents which could diminish the risk for cancer. This led to extensive studies on a variety of agents including isothiocyanates, indole-3-carbinol, *myo*-inositol, and related compounds. 2-Phenethyl isothiocyanate (PEITC), a potent inhibitor of carcinogenesis in several systems, was chosen for further development because of its natural occurrence and favorable preclinical profile. Together with our colleagues, we carried out an FDA-approved clinical trial of PEITC as an inhibitor of the metabolic activation of NNK in smokers, which showed modest inhibition, but a far greater effect on detoxification of common environmental agents such as benzene, a lead we are pursuing actively in a clinical trial of watercress, an abundant source of PEITC, to enhance detoxification of these agents.
 - a. **Hecht, S. S.**, Trushin, N., Rigotty, J., Carmella, S. G., Borukhova, A., Akerkar, S. A., and Rivenson, A. (1996) Complete inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced rat lung tumorigenesis and favorable modification of biomarkers by phenethyl isothiocyanate. *Cancer Epidemiol. Biomarkers Prev.* 5, 645-652.
 - b. **Hecht, S. S.**, Kassie, F., and Hatsukami, D. K. (2009) Chemoprevention of lung carcinogenesis in addicted smokers and ex-smokers. *Nat. Rev. Cancer* 9, 476-488. PMID: PMC3876956.
 - c. Yuan, J.-M., Stepanov, I., Murphy, S. E., Wang, R., Allen, S., Jensen, J., Strayer, L., Adams-Haduch, J., Carmella, S. G., Upadhyaya, P., Le, C., Kurzer, M., Nelson, H. H., Yu, M. C., Hatsukami, D. K., and **Hecht, S. S.** (2016) Clinical trial of 2-phenethyl isothiocyanate as an inhibitor of metabolic activation of a tobacco-specific lung carcinogen in cigarette smokers. *Cancer Prev. Res.* 9, 396-405. PMID: PMC4854759.

- d. Yuan, J. M., Murphy, S. E., Stepanov, I., Wang, R., Carmella, S. G., Nelson, H. H., Hatsukami, D., and **Hecht, S. S.** (2016) 2-Phenethyl isothiocyanate, *glutathione S-transferase M1* and *T1* polymorphisms, and detoxification of volatile organic carcinogens and toxicants in tobacco smoke. *Cancer Prev. Res.* 9, 598-606. PMCID: PMC4930697
5. *Expertise in tobacco carcinogenesis.* I have served on multiple U.S. and W.H.O. committees evaluating the tobacco and cancer problem and recommending solutions, and have regularly contributed to U.S. Surgeon General Reports on tobacco and cancer. I have written numerous invited reviews and book chapters on aspects of tobacco carcinogenesis. With Professor D. Hatsukami, I am currently editing a book entitled "Tobacco and Cancer: the Science and the Story" to be published in 2021 by World Scientific Press.
- a. **Hecht, S. S.** (1999) Tobacco smoke carcinogens and lung cancer. *J. Natl. Cancer Inst.* 91, 1194-1210. (cited 1349 times).
- b. **Hecht, S. S.** (2003) Tobacco carcinogens, their biomarkers, and tobacco-induced cancer. *Nature Rev. Cancer* 3, 733-744. (cited 883 times).
- c. **Hecht, S. S.**, and Szabo, E. (2014) Fifty years of tobacco carcinogenesis research: From mechanisms to early detection and prevention of lung cancer. *Cancer Prev. Res.* 7, 1-8. PMCID: PMC4296669
- d. **Hecht, S. S.** (2017) Oral cell DNA adducts as potential biomarkers for lung cancer susceptibility in cigarette smokers. *Chem Res Toxicol* 30, 367-375. PMCID: PMC5310195

Link to Bibliography Over 900 publications including more than 615 peer-reviewed journal articles and over 280 book chapters and related publications; control plus click to follow link
<http://www.ncbi.nlm.nih.gov/sites/myncbi/stephen.hecht.1/bibliography/41146177/public/?sort=date&direction=ascending>

Exhibit 2

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF NEW JERSEY
3 MDL No. 2875

4
5 IN RE: VALSARTAN, PRODUCTS)
LIABILITY LITIGATION)

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7)
8 TESTIMONY OF:)

9 Stephen Hecht, Ph.D.)
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12 August 17, 2021

13 9:00 a.m.

14 TRANSCRIPT of the stenographic notes of the video
15 recorded proceedings in the above-entitled matter, as
16 taken by and before Sara K. Killian, a Registered
17 Professional Reporter, Certified Court Reporter and Notary
18 Public, remotely via Zoom videoconferencing.
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<p style="text-align: right;">Page 2</p> <p>1 A P P E A R A N C E S :</p> <p>2</p> <p>3 MAZIE SLATER KATZ & FREEMAN, LLC</p> <p>4 Attorneys for Plaintiffs</p> <p>5 103 Eisenhower Parkway, Second Floor</p> <p>6 Roseland, New Jersey 07068</p> <p>7 BY: ADAM SLATER, ESQ.</p> <p>8 CHRISTOPHER GEDDIS, ESQ.</p> <p>9 JULIA SLATER, ESQ.</p> <p>10</p> <p>11</p> <p>12</p> <p>13 MARTIN HARDING & MAZZOTTI, LLP</p> <p>14 Attorneys for Plaintiffs</p> <p>15 100 Park Avenue Center, 16th Floor</p> <p>16 New York, New York 10017</p> <p>17 BY: ROSEMARIE RIDDELL BOGDAN, ESQ.</p> <p>18</p> <p>19</p> <p>20 GOLOMB & HONIK, PC</p> <p>21 Attorneys for Plaintiffs</p> <p>22 1835 Market Street, #2900</p> <p>23 Philadelphia, Pennsylvania 19103</p> <p>24 BY: RUBEN HONIK, ESQ.</p> <p>25</p>	<p style="text-align: right;">Page 4</p> <p>1 A P P E A R A N C E S: (cont'd)</p> <p>2</p> <p>3 GREENBERG TRAUIG, LLP</p> <p>4 Attorneys for Teva Pharmaceuticals USA</p> <p>5 333 SE 2nd Avenue, Suite 4400</p> <p>6 Miami, Florida 33131</p> <p>7 BY: STEPHEN FOWLER, ESQ.</p> <p>8 VICTORIA LOCKARD, ESQ.</p> <p>9</p> <p>10</p> <p>11</p> <p>12 WALSH PIZZI O'REILLY FALANGA</p> <p>13 Attorneys for Teva Pharmaceuticals USA</p> <p>14 One Riverfront Plaza</p> <p>15 1037 Raymond Boulevard, Suite 600</p> <p>16 Newark, New Jersey 07102</p> <p>17 BY: CHRISTINE GANNON, ESQ.</p> <p>18</p> <p>19</p> <p>20 CIPRIANI & WERNER, PC</p> <p>21 Attorneys for Aurobindo Pharma USA, Inc.</p> <p>22 450 Sentry Parkway, Suite 200</p> <p>23 Blue Bell, Pennsylvania 19422</p> <p>24 BY: JILL FERTEL, ESQ.</p> <p>25</p>
<p style="text-align: right;">Page 3</p> <p>1 A P P E A R A N C E S: (cont'd)</p> <p>2</p> <p>3 PIETRAGALLO GORDON ALFANO BOSICK & RASPANTI, LLP</p> <p>4 Attorneys for Mylan Pharmaceuticals Inc., Mylan</p> <p>5 Laboratories Ltd., Mylan Inc., and Mylan N.V.</p> <p>6 One Oxford Centre</p> <p>7 301 Grant Street</p> <p>8 Pittsburgh, Pennsylvania 15219</p> <p>9 BY: CLEM TRISCHLER, ESQ.</p> <p>10 FRANK STOY, ESQ.</p> <p>11 TIFFANY GRIMES, Paralegal</p> <p>12</p> <p>13</p> <p>14</p> <p>15 BARNES & THORNBURG, LLP</p> <p>16 Attorneys for CVS and Rite Aid</p> <p>17 11 South Meridian Street</p> <p>18 Indianapolis, Indiana 46204</p> <p>19 BY: KARA KAPKE, ESQ.</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 5</p> <p>1 A P P E A R A N C E S: (cont'd)</p> <p>2</p> <p>3 DUANE MORRIS, LLP</p> <p>4 Attorneys for Princeton Pharmaceutical Inc., Zhejiang</p> <p>5 Huahai Pharmaceutical Co., Ltd., Solco Healthcare</p> <p>6 US, LLC, Huahai US, Inc., Walmart Stores, Inc.,</p> <p>7 and Walgreen Co.</p> <p>8 1875 NW Corporate Boulevard, Suite 300</p> <p>9 Boca Raton, Florida 33431</p> <p>10 BY: PATRICK C. GALLAGHER, ESQ.</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15 HINSHAW & CULBERTSON, LLP</p> <p>16 Attorneys for HJ Harkins and Scigen</p> <p>17 53 State Street, 27th Floor</p> <p>18 Boston, Massachusetts 02109</p> <p>19 BY: KATHLEEN E. KELLY, ESQ.</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

<p style="text-align: right;">Page 6</p> <p>1 A P P E A R A N C E S: (cont'd)</p> <p>2</p> <p>3 FALKENBERG IVES, LLP</p> <p>4 Attorneys for Humana Pharmacy</p> <p>5 230 W. Monroe, Suite 2220</p> <p>6 Chicago, Illinois 60606</p> <p>7 BY: KIRSTEN IVES, ESQ.</p> <p>8</p> <p>9</p> <p>10</p> <p>11 HILL WALLACK, LLP</p> <p>12 Attorneys for Hetero Drugs Ltd. and Hetero Labs Ltd.</p> <p>13 21 Roszel Road</p> <p>14 Princeton, New Jersey 08543</p> <p>15 BY: NAKUL Y. SHAH, ESQ.</p> <p>16 CARLOS S. DeHART, ESQ.</p> <p>17</p> <p>18</p> <p>19</p> <p>20 BUCHANAN INGERSOLL & ROONEY, PC</p> <p>21 Attorneys for Albertson's LLC</p> <p>22 227 West Trade Street, Suite 600</p> <p>23 Charlotte, North Carolina 28202</p> <p>24 BY: CHRISTOPHER B. HENRY, ESQ.</p> <p>25</p>	<p style="text-align: right;">Page 8</p> <p>1 I N D E X</p> <p>2</p> <p>3 WITNESS EXAMINATION BY PAGE</p> <p>4 Dr. Hecht Mr. Trischler 12</p> <p>5 Mr. Fowler 309</p> <p>6 Ms. Kapke 390</p> <p>7</p> <p>8 E X H I B I T S</p> <p>9 EXHIBITS DESCRIPTION PAGE</p> <p>10 Exhibit 1 Expert Report of Stephen 18</p> <p>Hecht, Ph.D., 7/6/21</p> <p>11</p> <p>12 Exhibit 2 Curriculum vitae of 33</p> <p>Stephen Hecht, Ph.D.</p> <p>13 Exhibit 3 "Plaintiffs' Disclosure 36</p> <p>of Cancer Types"</p> <p>14</p> <p>15 Exhibit 4 "Comparative 67</p> <p>Tumorigenicity and DNA</p> <p>Methylation in F344 Rats</p> <p>16 by</p> <p>17 4-(Methylnitrosamino)-1-(</p> <p>3-pyridyl)-1-butanone and</p> <p>N-nitrosodimethylamine"</p> <p>18 by Stephen Hecht, et al</p> <p>19 Exhibit 5 Invoices 102</p> <p>20 Exhibit 6 "Pharmacokinetics of 113</p> <p>N-nitrosodimethylamine in</p> <p>beagles" by C.T. Gombar,</p> <p>et al</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p style="text-align: right;">Page 7</p> <p>1 A P P E A R A N C E S: (cont'd)</p> <p>2</p> <p>3 HUSCH BLACKWELL, LLP</p> <p>4 Attorneys for Express Script, Inc.</p> <p>5 190 Carondelet Plaza, Suite 600</p> <p>6 St. Louis, Missouri 63105</p> <p>7 BY: JAMES SPRUNG, ESQ.</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14 ALSO PRESENT:</p> <p>15 WILLIAM MILLER, Veritext Videographer</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 9</p> <p>1 E X H I B I T S</p> <p>2 EXHIBITS DESCRIPTION PAGE</p> <p>3 Exhibit 7 "The Production of 118</p> <p>Malignant Primary Hepatic</p> <p>4 Tumours in the Rat by</p> <p>Feeding</p> <p>5 Dimethylnitrosamine" by</p> <p>P.N. Magee and J.M.</p> <p>6 Barnes</p> <p>7 Exhibit 8 "Effects on 4080 Rats of 123</p> <p>Chronic Ingestion of</p> <p>8 N-Nitrosodiethylamine or</p> <p>N-Nitrosodimethylamine:</p> <p>9 A Detailed Dose-Response</p> <p>Study" by Richard Peto,</p> <p>10 et al</p> <p>11 Exhibit 9 "Pharmacokinetics of 125</p> <p>N-nitrosodimethylamine in</p> <p>swine" by C.T. Gombar, et</p> <p>12 al</p> <p>13</p> <p>14 Exhibit 10 Agents Classified by the 142</p> <p>IARC Monographs, Volumes</p> <p>1-123</p> <p>15</p> <p>16 Exhibit 11 "Information about 159</p> <p>Nitrosamine Impurities in</p> <p>Medications"</p> <p>17</p> <p>18 Exhibit 12 "Critical Review of Major 174</p> <p>Sources of Human Exposure</p> <p>to N-nitrosamines" by</p> <p>19 Adam J. Gushgari and Rolf</p> <p>U. Halden</p> <p>20</p> <p>21 Exhibit 13 "Nitrosamines as 199</p> <p>Impurities in Drugs,</p> <p>Health Risk Assessment</p> <p>22 and Mitigation Public</p> <p>Workshop"</p> <p>23</p> <p>24 Exhibit 14 "Permitted Daily Exposure 207</p> <p>Limits for Noteworthy</p> <p>N-nitrosamines" by George</p> <p>25 E. Johnson, et al</p>

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<p style="text-align: right;">Page 11</p> <p>1 EXHIBITS</p> <p>2 EXHIBITS DESCRIPTION PAGE</p> <p>3 Exhibit 23 Defendants' Notice of 309</p> <p>4 Videotaped Deposition of</p> <p>5 Exhibit 24 "Interspecies Scaling of 325</p> <p>6 the Pharmacokinetics of</p> <p>7 N-nitrosodimethylamine"</p> <p>8 by Charles Gombar, et al</p> <p>9 Exhibit 25 FDA Transcript, March 29, 383</p> <p>2021</p> <p>10 Exhibit 26 FDA Transcript, March 30, 383</p> <p>2021</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16 REQUESTS:</p> <p>17 Production requested Page 347</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 13</p> <p>1 This is the time and place set for</p> <p>2 the deposition of Dr. Steven Hecht. Dr.</p> <p>3 Hecht issued a report dated July 6th, 2021</p> <p>4 and we're here today to take his deposition</p> <p>5 on issues relating to causation opinions that</p> <p>6 Dr. Hecht has or may have or wishes to</p> <p>7 testify about in connection with the</p> <p>8 valsartan multi-district litigation.</p> <p>9 The report of July 6, 2021 includes</p> <p>10 opinions and potential areas of testimony</p> <p>11 that go beyond the issue of causation and get</p> <p>12 into what I would consider to be other</p> <p>13 liability issues.</p> <p>14 I believe the agreement of the</p> <p>15 parties is that any inquiry of Dr. Hecht on</p> <p>16 those issues unrelated to causation will be</p> <p>17 deferred until a later period of time in</p> <p>18 connection with this multi-district</p> <p>19 litigation. My deposition of Dr. Hecht and</p> <p>20 the defendant's deposition of Dr. Hecht today</p> <p>21 will be limited to causation opinions.</p> <p>22 Is that fair, Mr. Slater?</p> <p>23 MR. SLATER: Yes. This deposition</p> <p>24 will not address liability, but will address</p> <p>25 general causation.</p>

<p style="text-align: right;">Page 14</p> <p>1 MR. TRISCHLER: Understood and 2 agreed. 3 Thank you. 4 EXAMINATION BY 5 MR. TRISCHLER: 6 Q. Dr. Hecht, as I mentioned just a 7 moment ago, my name is Clem Trischler. I'm an 8 attorney. I represent the Mylan defendants and 9 the Defendants' Executive Committee in the 10 valsartan multi-district litigation that's pending 11 in the United States District Court for the 12 District of New Jersey. 13 You have been identified and 14 disclosed as an expert witness on behalf of the 15 plaintiffs in this litigation. 16 Are you aware of that? 17 A. Yes. 18 Q. Obviously, we're gathered to take 19 your deposition on causation issues relevant to 20 this litigation. I take it that you've given 21 deposition testimony before? 22 A. Yes. 23 Q. Given that fact, I'll refrain from 24 going into a detailed discussion of what the 25 deposition process is, but suffice it to say</p>	<p style="text-align: right;">Page 16</p> <p>1 A. No. 2 Q. Are you using a laptop or a desktop 3 computer to participate in this deposition? 4 A. It's a laptop. 5 Q. Do you have any other electronic 6 devices with you in the room as you give this 7 deposition other than the laptop on which you're 8 using to communicate with me? 9 A. Yes. I have my desktop and my phone. 10 Q. Would it be possible for you to turn 11 your desktop and phone off during the deposition? 12 A. I can. I was going to use the 13 desktop to view any of the papers that we're going 14 to discuss under sender say. I was given a link 15 to Novac Trial Services that would have the -- a 16 lot of the documents, so I thought that would be 17 convenient to look at, but I can turn it off. 18 Q. Well, that's -- that's all right. 19 What I want to make sure is that 20 you're not receiving communications from any 21 source on other electronic devices during the time 22 of the deposition. 23 A. No. 24 Q. All right. 25 What's your occupation?</p>
<p style="text-align: right;">Page 15</p> <p>1 myself and perhaps some other lawyers are going to 2 be asking you questions today and the answers that 3 you are providing are answers under oath and under 4 penalty of perjury. 5 Do you understand that? 6 A. Yes. 7 Q. I presume then that the answers that 8 you provide to my questions today will be honest 9 and truthful and to the best of your ability? 10 A. Yes. 11 Q. Tell us your full name, sir. 12 A. Stephen Samuel Hecht. 13 Q. What's your professional address, 14 Dr. Hecht? 15 A. Masonic Cancer Center, University of 16 Minnesota, Minneapolis, 55455. 17 Q. Where are you physically located 18 today as you give your deposition? 19 A. I'm in the Cancer and Cardiovascular 20 Research Building on the university campus. 21 Q. And the university campus being the 22 campus of the University of Minnesota? 23 A. Yes. 24 Q. Is anyone in the room with you as you 25 give your deposition testimony today?</p>	<p style="text-align: right;">Page 17</p> <p>1 A. I'm a professor. Walin Professor of 2 Cancer Prevention, University of Minnesota. 3 Q. You indicated in response to one of 4 my earlier questions that you were, in fact, 5 retained by the plaintiffs in the valsartan 6 litigation. 7 True? 8 A. Yes. 9 Q. When were you initially retained to 10 work for the plaintiffs in this litigation? 11 A. I don't have the exact date. It's 12 about two years ago. 13 Q. I was provided with some of your 14 invoices within the last couple of days and I'll 15 represent to you that the earliest entry that I 16 saw on your invoices was September 4, 2019. 17 A. Yes, that sounds about right. 18 Q. So would that entry refresh your 19 recollection as to the approximate period of time 20 when you were initially retained in this 21 litigation? 22 A. About two years. 23 Q. So about two years ago would be 24 September 2019; true? 25 A. Yes.</p>

5 (Pages 14 - 17)

<p style="text-align: right;">Page 18</p> <p>1 Q. Who initially retained you?</p> <p>2 A. Mr. Slater.</p> <p>3 Q. When you were retained by Mr. Slater,</p> <p>4 were you asked to analyze data and provide an</p> <p>5 opinion on whether levels of NDMA and NDEA</p> <p>6 observed in valsartan-containing medication was</p> <p>7 capable of causing cancer in humans?</p> <p>8 A. Yes.</p> <p>9 Q. Did you attempt to answer that</p> <p>10 question in the July 6, 2021 report that's been</p> <p>11 filed in this case?</p> <p>12 A. Yes.</p> <p>13 MR. TRISCHLER: I'm going to mark as</p> <p>14 Exhibit 1 to the deposition a copy of your</p> <p>15 July 6th, 2021 report.</p> <p>16 (Whereupon, Exhibit 1 was marked for</p> <p>17 identification.)</p> <p>18 Q. Do you have that with you, Dr. Hecht.</p> <p>19 A. Yes, I do.</p> <p>20 THE VIDEOGRAPHER: Counsel, would you</p> <p>21 like me to pull that up on the screen?</p> <p>22 MR. TRISCHLER: If need be. It</p> <p>23 might -- let's --</p> <p>24 MR. SLATER: He has it in hard copy,</p> <p>25 I think.</p>	<p style="text-align: right;">Page 20</p> <p>1 the report. It could have been his wife, it</p> <p>2 could have been an associate professor. It</p> <p>3 could have been anyone, Adam.</p> <p>4 MR. SLATER: So anyone other than a</p> <p>5 lawyer?</p> <p>6 I'll allow him to answer.</p> <p>7 Q. Did anyone assist you in the</p> <p>8 preparation of this report, sir?</p> <p>9 A. Yes. I was assisted by Mr. Slater.</p> <p>10 Q. I'm not interested in what assistance</p> <p>11 Mr. Slater may have provided, so other than</p> <p>12 Mr. Slater, did anyone assist you in the</p> <p>13 preparation of this report?</p> <p>14 A. No.</p> <p>15 Q. Did anyone write any sections of this</p> <p>16 report for you?</p> <p>17 A. No.</p> <p>18 Q. In the conclusion to your report that</p> <p>19 appears on page 27, you write "These nitrosamines</p> <p>20 in valsartan-containing medication posed an</p> <p>21 unacceptable risks of causing or substantially</p> <p>22 contributing to the causation of cancer for those</p> <p>23 ingesting the valsartan."</p> <p>24 Did I read that correctly?</p> <p>25 A. Presumably.</p>
<p style="text-align: right;">Page 19</p> <p>1 MR. TRISCHLER: That's why I'm asking</p> <p>2 if he has it. I'd rather just work with the</p> <p>3 doctor if he has it.</p> <p>4 Q. You have the report that we marked as</p> <p>5 Exhibit 1, sir?</p> <p>6 A. Yes.</p> <p>7 Q. All right.</p> <p>8 Is that your signature that appears</p> <p>9 on the first page of that report?</p> <p>10 A. Yes.</p> <p>11 Q. Did you prepare this report?</p> <p>12 A. Yes.</p> <p>13 Q. Is it the product of your work?</p> <p>14 A. Yes.</p> <p>15 Q. Did anyone assist you in the</p> <p>16 preparation of this report?</p> <p>17 MR. SLATER: Clem, objection.</p> <p>18 Are you trying to get into areas that</p> <p>19 are obviously covered by work product</p> <p>20 privilege? I mean, the preparation of the</p> <p>21 report is work product. Drafts are the not</p> <p>22 discoverable, so I'm not sure where we're</p> <p>23 going with this.</p> <p>24 MR. TRISCHLER: I didn't ask about</p> <p>25 drafts. I asked if anyone helped him with</p>	<p style="text-align: right;">Page 21</p> <p>1 Q. Is there a difference in your mind</p> <p>2 between an exposure that creates an unacceptable</p> <p>3 risk of contributing to cancer causation and an</p> <p>4 exposure that definitely causes cancer?</p> <p>5 MR. SLATER: Objection to the form of</p> <p>6 the question.</p> <p>7 You can answer.</p> <p>8 A. Repeat the question.</p> <p>9 Q. Sure.</p> <p>10 Is there a difference in your mind</p> <p>11 between an exposure that creates an unacceptable</p> <p>12 risk of contributing to cancer causation and an</p> <p>13 exposure that definitely causes cancer?</p> <p>14 MR. SLATER: Same objection.</p> <p>15 You can answer.</p> <p>16 A. Yes.</p> <p>17 Q. What's the difference in your mind?</p> <p>18 MR. SLATER: Same objection.</p> <p>19 You can answer.</p> <p>20 A. We are using the available data to</p> <p>21 determine whether it's probable or even likely</p> <p>22 that certain exposure could cause cancer versus</p> <p>23 another situation where we know perhaps a person</p> <p>24 has been treated with a chemotherapeutic drug that</p> <p>25 has carcinogenic side effects where you know on an</p>

<p style="text-align: right;">Page 22</p> <p>1 individual basis that you know the 2 chemotherapeutic drug caused perhaps a second 3 cancer, a different cancer than the one the person 4 was being treated for. 5 I don't know. Does that answer your 6 question? 7 Q. I'm not sure. 8 A. So in this particular case, we don't 9 know about the individual exposure and outcome. 10 All we know about is that the valsartan drug 11 contained a carcinogen. Whereas in the other case 12 that you mentioned, I believe what you were saying 13 is we know if we administer a certain cancer 14 causing agent to a given person and that person 15 gets cancer, then we know cause and effect in that 16 individual. 17 Is that your question? 18 Q. I'm not sure that was my question, 19 but I think what I heard you say is that in some 20 instances, we can tell cause and effect with 21 reasonable certainty and some instances, we 22 cannot? 23 MR. SLATER: Objection. 24 You can answer. 25 A. I don't know what you mean by</p>	<p style="text-align: right;">Page 24</p> <p>1 caused cancer? 2 MR. SLATER: Objection. 3 Multiple reasons. 4 You can answer, Dr. Hecht. 5 A. They increased the risk of cancer. 6 Q. Now, there are lots of risk factors 7 for cancer; true? 8 A. Yes. 9 Q. Old age is a risk factor, correct? 10 A. Yes. 11 Q. People over the age of 50 are at an 12 increased risk of cancer; true? 13 A. Correct. 14 Q. People over the age of 50 are at an 15 increased risk of cancer regardless whether they 16 take valsartan; true? 17 A. Yes. 18 Q. People over the age of 50 are at an 19 increased risk of cancer regardless of whether 20 they took valsartan containing small amounts of 21 nitrosamines; true? 22 MR. SLATER: Objection. 23 You can answer. 24 A. Yes. 25 MR. SLATER: Dr. Hecht, one second.</p>
<p style="text-align: right;">Page 23</p> <p>1 reasonable certainty. 2 Q. Well, expert opinions -- strike that. 3 Expert witnesses in civil litigation 4 of this nature are supposed to provide scientific 5 testimony to a reasonable degree of scientific 6 certainty. 7 Is that your intention today? 8 A. Yes. 9 Q. So to a reasonable degree of 10 scientific certainty, what I'm asking you is are 11 there instances where we can definitively 12 determine the cause of cancer and instances where 13 we could not? 14 MR. SLATER: Objection. 15 You can answer. 16 A. Yes, there are instances where we can 17 definitively determine the cause of cancer. 18 Q. So what I'm trying to understand, 19 sir, is the opinion that you intend to offer in 20 this case. 21 Did NDMA and NDEA in 22 valsartan-containing medications increase the risk 23 of cancer or do you intend to offer the opinion 24 that small amounts of nitrosamines observed in the 25 valsartan-containing medications definitively</p>	<p style="text-align: right;">Page 25</p> <p>1 Just give a pause because he's going pretty 2 quick and I need to have a little time to 3 place my form objections to the questions and 4 then I would expect I'll go ahead and say you 5 could answer every time or virtually every 6 time, but just give a little pause so I don't 7 step on your answer. 8 Okay? 9 THE WITNESS: Okay. 10 Q. That's fair, Dr. Hecht. I probably 11 should have told you at the beginning, that 12 especially taking these depositions remotely, we 13 have to be careful not all to speak at the same 14 time because if you and I or Adam and I are 15 speaking at the same time, the audio tends to go 16 out and the court reporter can't take everything 17 down. If you could try to pause before -- after I 18 finish my question, give Adam a chance to 19 interject if he needs to, that will make things go 20 a lot more smoothly. My fault for not covering. 21 Okay? 22 A. Okay. 23 Q. So is a family history of cancer also 24 a risk factor for cancer? 25 A. Yes.</p>

<p style="text-align: right;">Page 26</p> <p>1 Q. Is tobacco use a risk factor for 2 cancer? 3 A. Yes. 4 Q. Is alcohol use a risk factor for 5 cancer? 6 A. Yes. 7 Q. Is obesity a risk factor for cancer? 8 A. Yes. 9 Q. What you are saying here today or 10 what your opinion that you intend to offer in this 11 case is is that increased nitrosamine intake is 12 also a risk factor for cancer, you believe? 13 A. Yes. 14 Q. I assume we could also agree right 15 off the bat, Dr. Hecht, that just because 16 something is a risk factor doesn't mean that it 17 caused cancer? 18 A. Correct. 19 Q. You can be 400 pounds, but that 20 doesn't mean that's the reason why you develop 21 lung cancer; true? 22 A. Correct. 23 Q. Do you also understand and can we 24 agree that the question of whether a substance is 25 capable of causing cancer is dependent on dose and</p>	<p style="text-align: right;">Page 28</p> <p>1 know about that. 2 Q. Well, let me give you a for instance. 3 Water is a life-sustaining substance, 4 correct? 5 A. Yes. 6 Q. However, water can be deadly when 7 it's consumed to excess; true? 8 A. Yes. 9 Q. So there are -- you didn't want to 10 agree with virtually all, but there are many 11 substances that have the capacity to be harmful at 12 some level; true? 13 A. Yes. 14 Q. And since there are many substances 15 that have the capacity to be harmful at some 16 level, looking at exposure levels, dose and 17 duration would be a reasonable and necessary 18 approach when evaluating cancer causation; agreed? 19 A. Yes. 20 Q. The question in this litigation to be 21 answered is not whether nitrosamines can cause 22 harm at any level. 23 Do you understand the question that 24 we're interested in getting at is whether there's 25 credible scientific evidence that the small</p>
<p style="text-align: right;">Page 27</p> <p>1 duration of exposure? 2 A. Yes. 3 Q. And -- 4 MR. SLATER: Belated objection. 5 It went a little quick, but you could 6 continue. 7 Q. The reason I thought we could agree 8 on that is you seemed to acknowledge that fact in 9 the conclusion of your report on page 27 when you 10 write that any increased risk would be 11 commensurate with the impurity level, the dose and 12 the period of use. 13 Is that right? 14 A. Yes. 15 Q. Are you familiar with the old adage 16 that "The dose makes the poison"? 17 A. Yes. 18 Q. Do you agree with that statement? 19 A. Yes. 20 Q. All substances -- strike that. 21 Virtually all substances known to man 22 have a capacity to be toxic at some level; true? 23 MR. SLATER: Objection. 24 You can answer. 25 A. All substances known to man? I don't</p>	<p style="text-align: right;">Page 29</p> <p>1 amounts of NDMA that was contained in 2 valsartan-containing medications can cause cancer 3 in humans. 4 Can we agree on that? 5 MR. SLATER: Objection to the form of 6 the question. 7 You can answer. 8 A. Yes. 9 Q. I guess a second question to be 10 answered is whether small tiny amounts of NDEA 11 found in valsartan-containing medications can 12 cause cancer in humans, right? 13 MR. SLATER: Objection to the form of 14 the question. 15 You can answer. 16 A. Yes. 17 Q. Since we can agree on the questions 18 to be answered, I take it that what the reason 19 that you're here is that you were retained by 20 Mr. Slater and the lawyers and the plaintiff group 21 to help analyze and provide answers to those two 22 questions. 23 Is that accurate? 24 MR. SLATER: Objection. 25 You can answer.</p>

<p style="text-align: right;">Page 30</p> <p>1 A. Yes.</p> <p>2 Q. So in broad strokes, Dr. Hecht, tell</p> <p>3 me generally what work you did to answer those two</p> <p>4 questions.</p> <p>5 MR. SLATER: Objection.</p> <p>6 You can answer.</p> <p>7 A. Well, I looked to the literature and</p> <p>8 all of the data regarding the contamination of</p> <p>9 valsartan with dimethylnitrosamine,</p> <p>10 dimethylnitrosamine. My conclusion was that it</p> <p>11 posed -- that it should not have been there, first</p> <p>12 of all, and it posed an unacceptable risk to</p> <p>13 people using these medications.</p> <p>14 Q. Let me stop you. It sounds like you</p> <p>15 were finished anyway, Dr. Hecht. If my question</p> <p>16 was unclear, I apologize. I wasn't really</p> <p>17 interested in getting at all of your opinions</p> <p>18 right now.</p> <p>19 My question was if you could just</p> <p>20 tell me in a general fashion what work you did to</p> <p>21 answer the questions or to form your opinions.</p> <p>22 You told me that so far you looked up</p> <p>23 literature, correct?</p> <p>24 A. Yes.</p> <p>25 Q. You told me that you looked at some</p>	<p style="text-align: right;">Page 32</p> <p>1 and documents that were provided to you by</p> <p>2 Mr. Slater and his team, is there anything else</p> <p>3 you did to sit down and write the report that we</p> <p>4 marked as Exhibit 1?</p> <p>5 MR. SLATER: Objection.</p> <p>6 You can answer.</p> <p>7 A. Anything else that I did? I, you</p> <p>8 know, depended on my experience and knowledge of</p> <p>9 the literature about nitrosamine carcinogenesis.</p> <p>10 So I depended on that knowledge, I drew on it to</p> <p>11 write the report.</p> <p>12 Q. Sure.</p> <p>13 Now, I understand -- and I'm going to</p> <p>14 get into your background in a little bit -- but I</p> <p>15 understand you drew upon and relied upon your</p> <p>16 background in reaching conclusions based on your</p> <p>17 review of the literature and review of the</p> <p>18 documents provided to you by Mr. Slater.</p> <p>19 That's what you're telling me,</p> <p>20 correct?</p> <p>21 A. Yes.</p> <p>22 Q. Was there any other work that you</p> <p>23 actively did to prepare the report other than what</p> <p>24 we've described?</p> <p>25 A. I'm not sure exactly what you mean by</p>
<p style="text-align: right;">Page 31</p> <p>1 data on nitrosamine levels in valsartan products</p> <p>2 from some manufacturers, correct?</p> <p>3 MR. SLATER: Objection.</p> <p>4 Mischaracterization of the testimony.</p> <p>5 You can answer.</p> <p>6 A. Yes. I looked at what's in the</p> <p>7 literature and what's in the documents that I was</p> <p>8 given.</p> <p>9 Q. Okay.</p> <p>10 So again, I'm just looking for broad</p> <p>11 strokes in terms of what work you did to sit down</p> <p>12 and write this report that we marked as Exhibit 1.</p> <p>13 You've told me looking at literature</p> <p>14 and looking at documents and I assume we're</p> <p>15 talking about company documents that were provided</p> <p>16 to you by Mr. Slater and his team, right?</p> <p>17 A. Yes, in part. And also published</p> <p>18 literature like the EMA report.</p> <p>19 Q. Okay.</p> <p>20 A. Other publications in the open</p> <p>21 literature that have discussed this.</p> <p>22 Q. Okay.</p> <p>23 My apologies for interrupting you</p> <p>24 there briefly.</p> <p>25 Other than looking at the literature</p>	<p style="text-align: right;">Page 33</p> <p>1 other -- I wrote the report based on the sources</p> <p>2 that I had.</p> <p>3 (Whereupon, Exhibit 2 was marked for</p> <p>4 identification.)</p> <p>5 Q. So let's -- let me ask you some</p> <p>6 questions about your background then.</p> <p>7 I have attached as Exhibit 2 a copy</p> <p>8 of your CV, which contains a rather large</p> <p>9 bibliography.</p> <p>10 Do you happen to have a copy of your</p> <p>11 CV with you, Dr. Hecht?</p> <p>12 A. It's on my computer. I don't have --</p> <p>13 MR. SLATER: It's also attached to</p> <p>14 the report, Doctor. Or it should be.</p> <p>15 Q. Well, if you need to refer to it to</p> <p>16 answer my questions, feel free.</p> <p>17 Okay?</p> <p>18 A. Okay.</p> <p>19 Q. But does the -- can you tell me</p> <p>20 whether the CV that we've marked as Exhibit 2 and</p> <p>21 which is attached to your report contains an</p> <p>22 accurate list of your professional qualifications?</p> <p>23 A. Yes.</p> <p>24 Q. Is it complete and up to date as far</p> <p>25 as you know?</p>

<p style="text-align: right;">Page 34</p> <p>1 A. Yes.</p> <p>2 Q. Is there anything that you'd like to</p> <p>3 add or remove from the CV?</p> <p>4 A. No.</p> <p>5 Q. Based on my review of your CV, it</p> <p>6 appears your formal education is in the field of</p> <p>7 chemistry; is that true?</p> <p>8 A. Yes.</p> <p>9 Q. You have a bachelor's degree in</p> <p>10 chemistry from Duke University; true?</p> <p>11 A. Correct.</p> <p>12 Q. And a PhD in organic chemistry that</p> <p>13 you obtained in 1968, correct?</p> <p>14 A. Right.</p> <p>15 Q. Did you have to write a thesis to</p> <p>16 obtain that PhD?</p> <p>17 A. Yes.</p> <p>18 Q. What was the subject matter of your</p> <p>19 thesis?</p> <p>20 A. The thesis was divided into two</p> <p>21 parts. The first part had to do with transannular</p> <p>22 carbene reactions. I'm not sure if you want me to</p> <p>23 go into detail about that.</p> <p>24 Q. That's all right.</p> <p>25 A. The second part dealt with the</p>	<p style="text-align: right;">Page 36</p> <p>1 pathologist; agreed?</p> <p>2 A. Yes.</p> <p>3 Q. Are you a medical doctor?</p> <p>4 A. No.</p> <p>5 Q. Since you're not a medical doctor, I</p> <p>6 take it you do not diagnose cancer in patients,</p> <p>7 correct?</p> <p>8 A. Correct.</p> <p>9 Q. Have you ever diagnosed a patient</p> <p>10 with esophageal cancer?</p> <p>11 A. No.</p> <p>12 Q. Have you ever diagnosed a patient</p> <p>13 with colorectal cancer?</p> <p>14 A. No.</p> <p>15 MR. TRISCHLER: I'm going to mark as</p> <p>16 Exhibit 3 a document that's entitled</p> <p>17 "Plaintiffs' Disclosure of Cancer Types."</p> <p>18 To our technician, this is one you</p> <p>19 can put up on the screen for me.</p> <p>20 (Whereupon, Exhibit 3 was marked for</p> <p>21 identification.)</p> <p>22 Q. Are you able to see that document,</p> <p>23 Dr. Hecht?</p> <p>24 A. Maybe you could make it a little</p> <p>25 larger.</p>
<p style="text-align: right;">Page 35</p> <p>1 photolysis of phenoxy compounds.</p> <p>2 Q. Sounds rivetting.</p> <p>3 A. Yes.</p> <p>4 Q. That was a poor attempt at humor.</p> <p>5 A. Yes, I know.</p> <p>6 Q. Did your thesis touch on</p> <p>7 nitrosamines?</p> <p>8 A. No.</p> <p>9 Q. May I ask your age, sir?</p> <p>10 A. Seventy-eight.</p> <p>11 Q. You mentioned earlier when I asked</p> <p>12 you your occupation, you indicated you're a</p> <p>13 professor, so currently you're in academia, right?</p> <p>14 A. Correct.</p> <p>15 Q. Are you an employee of the University</p> <p>16 of Minnesota?</p> <p>17 A. Yes.</p> <p>18 Q. And so you draw a salary from the</p> <p>19 university; is that right?</p> <p>20 A. Yes.</p> <p>21 Q. According to the CV, you're a</p> <p>22 professor in the Department of Laboratory Medicine</p> <p>23 and Pathology.</p> <p>24 A. Correct.</p> <p>25 Q. To be clear, though, you were not a</p>	<p style="text-align: right;">Page 37</p> <p>1 Q. I can't, but there's --</p> <p>2 THE VIDEOGRAPHER: Is there a</p> <p>3 specific section you'd like me to blow up?</p> <p>4 MR. TRISCHLER: Just the text in the</p> <p>5 middle.</p> <p>6 THE WITNESS: Okay.</p> <p>7 Q. Have you ever seen this document</p> <p>8 before, sir?</p> <p>9 A. Let me just read it first.</p> <p>10 Okay?</p> <p>11 Q. Sure.</p> <p>12 (Witness reviews document)</p> <p>13 A. No, I've not.</p> <p>14 Q. I'll represent to you that this is a</p> <p>15 disclosure that was filed by the plaintiffs in</p> <p>16 this litigation. It's a list of cancer types that</p> <p>17 have been placed at issue in this litigation.</p> <p>18 Okay?</p> <p>19 A. Okay.</p> <p>20 Q. Take a look.</p> <p>21 Do you see there are 13 cancer types</p> <p>22 listed? Do you see that?</p> <p>23 A. Yes.</p> <p>24 Q. Have you ever diagnosed any of these</p> <p>25 cancer types in any patient?</p>

<p style="text-align: right;">Page 38</p> <p>1 A. No.</p> <p>2 Q. Have you ever treated a cancer</p> <p>3 patient?</p> <p>4 A. No.</p> <p>5 Q. Going back to your role at the</p> <p>6 University of Minnesota, are you actively teaching</p> <p>7 at the moment?</p> <p>8 A. No.</p> <p>9 Q. Are you going to be teaching any</p> <p>10 courses in the 2021/2022 academic year?</p> <p>11 A. No.</p> <p>12 Q. When was the last time you taught a</p> <p>13 graduate level course?</p> <p>14 A. That's about ten years ago.</p> <p>15 Q. What was the course you taught some</p> <p>16 ten years ago?</p> <p>17 A. Chemical carcinogenesis.</p> <p>18 Q. Did you use a textbook for that</p> <p>19 course?</p> <p>20 A. No. We used the current literature.</p> <p>21 Q. Who were you teaching that graduate</p> <p>22 level course to? Was it medical students at the</p> <p>23 medical school or was it in some other</p> <p>24 environment?</p> <p>25 A. It was a mixture that -- there</p>	<p style="text-align: right;">Page 40</p> <p>1 A. Yes.</p> <p>2 Q. Have you ever taught an undergraduate</p> <p>3 course at the University of Minnesota?</p> <p>4 A. No.</p> <p>5 Q. Are you a full-time employee at this</p> <p>6 point or have you slowed down?</p> <p>7 A. No, I'm a full-time employee.</p> <p>8 MR. TRISCHLER: You can remove that</p> <p>9 exhibit, sir.</p> <p>10 Thank you.</p> <p>11 Q. Are you actively involved in any</p> <p>12 research projects at the moment?</p> <p>13 A. Yes, I am.</p> <p>14 Q. I think in your report that's marked</p> <p>15 as Exhibit 1 to this deposition you indicate at</p> <p>16 the bottom of page two that you are the principal</p> <p>17 investigator on three RO1 grants --</p> <p>18 A. RO1.</p> <p>19 Q. Correct?</p> <p>20 A. Yes.</p> <p>21 Q. By the way, the Masonic Cancer Center</p> <p>22 is designated as a comprehensive cancer center,</p> <p>23 correct?</p> <p>24 A. Correct.</p> <p>25 Q. I think that's a designation given by</p>
<p style="text-align: right;">Page 39</p> <p>1 weren't medical students.</p> <p>2 Q. Was it a graduate level course in</p> <p>3 some --</p> <p>4 A. In carcinogenesis. The students came</p> <p>5 from different programs in the university, but</p> <p>6 there weren't medical students. There were</p> <p>7 graduate students in medicinal chemistry or from</p> <p>8 the St. Paul campus on nutrition.</p> <p>9 Q. Thank you.</p> <p>10 I'm trying to get an understanding</p> <p>11 was it a class that was offered by the Department</p> <p>12 of Chemistry, the Department of Biology. Help me</p> <p>13 understand that, if you can.</p> <p>14 A. No, it was a graduate course in --</p> <p>15 actually, I've forgotten exactly which division it</p> <p>16 was listed in. I don't recall whether it was</p> <p>17 medicinal chemistry or whether it was in the C</p> <p>18 fans, the food and nutrition. I'm sorry. I don't</p> <p>19 remember.</p> <p>20 Q. That's okay. It's been ten years --</p> <p>21 I understand it's been ten years since you offered</p> <p>22 the course, correct, or taught the course?</p> <p>23 A. Yes.</p> <p>24 Q. Has it been ten years since you've</p> <p>25 been in the classroom at Minnesota?</p>	<p style="text-align: right;">Page 41</p> <p>1 the National Cancer Institute?</p> <p>2 A. Correct.</p> <p>3 Q. And Masonic would be one of over 50</p> <p>4 hospital systems over the country that have been</p> <p>5 so designated, right?</p> <p>6 A. About 50, yeah.</p> <p>7 Q. The National Cancer Institute has</p> <p>8 also designated seven laboratory centers across</p> <p>9 the country that do cutting edge cancer-related</p> <p>10 research, correct?</p> <p>11 A. Right. Those are laboratory centers.</p> <p>12 Comprehensive center includes not only laboratory</p> <p>13 research, but also treatment.</p> <p>14 Q. But Masonic is not one of the seven</p> <p>15 laboratory cancer centers designated --</p> <p>16 A. It's a comprehensive center, which</p> <p>17 includes laboratory work.</p> <p>18 Q. Going back then to the RO1 grants,</p> <p>19 these are projects that are funded by federal</p> <p>20 grants; is that right?</p> <p>21 A. Yes.</p> <p>22 Q. To whom were the three RO1 grants</p> <p>23 that you reference in your report issued?</p> <p>24 A. Well, I'm the principal investigator,</p> <p>25 but the grants are actually issued to the</p>

<p style="text-align: right;">Page 42</p> <p>1 University of Minnesota.</p> <p>2 Q. Can you describe the subject of those</p> <p>3 three current grants?</p> <p>4 A. Yes. One of them involves the</p> <p>5 mechanisms and prevention of tobacco-induced</p> <p>6 cancer caused by a group of carcinogens in tobacco</p> <p>7 products that we discovered and have worked on for</p> <p>8 many years called tobacco specific nitrosamines.</p> <p>9 The second grant --</p> <p>10 Q. I'm sorry.</p> <p>11 Would those be NNN and NNK?</p> <p>12 A. Correct. Do you want me to go on or</p> <p>13 do you want me to --</p> <p>14 Q. Yes, please.</p> <p>15 A. The second grant has to do with the</p> <p>16 carcinogens and toxicants that are possibly</p> <p>17 omitted from e-cigarettes that are present in</p> <p>18 e-cigarette paper and could be taken up by people</p> <p>19 who use these products.</p> <p>20 The third one is a clinical trial of</p> <p>21 watercress for -- to enhance the detoxification of</p> <p>22 environmental toxicants and carcinogens.</p> <p>23 Those are the three RO1 grants. I'm</p> <p>24 also the PI of a program project grant on the</p> <p>25 ethnic differences in cancer risk due to cigarette</p>	<p style="text-align: right;">Page 44</p> <p>1 effect in cigarette smokers as it did in</p> <p>2 laboratory animals, whether it could therefore be</p> <p>3 used as a chemo-preventative agent in people who</p> <p>4 couldn't stop smoking because they're addicted to</p> <p>5 nicotine. This compound was able to prevent</p> <p>6 cancer in animals treated with tobacco specific</p> <p>7 nitrosamines, as I mentioned.</p> <p>8 So in this clinical trial, we found</p> <p>9 that PEITC did, in fact, decrease the metabolic</p> <p>10 activation of NNK in smokers, which was the</p> <p>11 hypothesized result. But the decrease was, while</p> <p>12 significant, was quite small.</p> <p>13 However, in the same trial, we found</p> <p>14 that certain people who took the PEITC had a great</p> <p>15 increase in their ability to detoxify</p> <p>16 environmental toxicants like benzene. This formed</p> <p>17 the basis for the watercress study because</p> <p>18 watercress is a great source of PEITC. Just a</p> <p>19 salad-sized portion of watercress will, when you</p> <p>20 eat it, when you chew it, will release 20 to</p> <p>21 30 milligrams of PEITC, which was similar to the</p> <p>22 dose of the pure compound we had used in the study</p> <p>23 that I described.</p> <p>24 So that's what gave rise to the</p> <p>25 watercress trial.</p>
<p style="text-align: right;">Page 43</p> <p>1 smoking.</p> <p>2 Q. Okay.</p> <p>3 Thank you for the descriptions.</p> <p>4 The third one -- the third RO1 grant</p> <p>5 you mentioned, I'm not sure if I didn't hear you</p> <p>6 or didn't understand you. You said it was a</p> <p>7 clinical trial involving what?</p> <p>8 A. Watercress.</p> <p>9 Q. Forgive my ignorance.</p> <p>10 What's watercress?</p> <p>11 A. It's a plant.</p> <p>12 Q. Okay.</p> <p>13 A. It's a common food that people use in</p> <p>14 salads. Watercress.</p> <p>15 Q. Is it carcinogenic?</p> <p>16 A. No. Not at all.</p> <p>17 Q. What does the clinical trial involve?</p> <p>18 A. So we found over the years in other</p> <p>19 studies that we've done that a compound that's</p> <p>20 present in watercress called PEITC -- or phenethyl</p> <p>21 isothiocyanate -- can prevent lung cancer in rats</p> <p>22 and mice treated with tobacco carcinogens. Based</p> <p>23 on that work, we performed a clinical trial with</p> <p>24 our colleagues here at the University of Minnesota</p> <p>25 to determine whether PEITC would have a similar</p>	<p style="text-align: right;">Page 45</p> <p>1 Q. All right. I understand what you're</p> <p>2 doing now in that study. I appreciate the</p> <p>3 details.</p> <p>4 So you've now told me about your</p> <p>5 current RO1 grants and your --</p> <p>6 A. Grant project.</p> <p>7 Q. -- correct.</p> <p>8 A. Yes.</p> <p>9 Q. Do any of your current RO1 grants or</p> <p>10 the program project grant deal specifically with</p> <p>11 NDMA or NDEA?</p> <p>12 A. The one on tobacco specific</p> <p>13 nitrosamines, while the specific names aren't</p> <p>14 dealing specifically with NDMA, it's closely</p> <p>15 related to NNK in terms of its mechanistic</p> <p>16 properties.</p> <p>17 So the answer -- the short answer to</p> <p>18 your question is no, but the longer answer is that</p> <p>19 yes, it's closely related.</p> <p>20 Q. Well, I understand that NDMA and NNN</p> <p>21 or NNK might be chemically related, but my</p> <p>22 question was are these grants dealing specifically</p> <p>23 with NDMA or NDEA grant research?</p> <p>24 A. Not specifically. Not in the</p> <p>25 specific names.</p>

<p style="text-align: right;">Page 46</p> <p>1 Q. Have you ever been involved in any 2 federally-funded research products dealing 3 directly with the carcinogenicity of NDMA? 4 A. Yes. 5 Q. Can you tell me about those, please? 6 A. Well, when I was still at the 7 American Health Foundation, we did studies that 8 compared the carcinogenicity and metabolism of 9 NDMA and NNK. We did this because NNK was a 10 relatively -- a relatively new carcinogen that 11 hadn't been explored with a regard to its 12 carcinogenic properties and mechanisms of action, 13 whereas NDMA has been known as a carcinogen since 14 1956. 15 So since NDMA was such a 16 well-established carcinogen, we thought it would 17 be important to compare some of the properties of 18 NNK and NDMA, so we did do those studies. 19 Q. I think that was back in the 1980s, 20 you said? 21 A. Yes. 22 Q. It was a comparative analysis of the 23 potency of NDMA to NNK? 24 A. Yes. 25 Q. You published the results of those --</p>	<p style="text-align: right;">Page 48</p> <p>1 Q. Have you ever been involved in any 2 research projects devoted to analyzing the 3 mechanism of action of cancer induction from NDEA? 4 A. Not directly. 5 Q. Since you don't have a medical 6 degree, I take it you're not Board Certified in 7 oncology, radiology or any other medical 8 discipline, right? 9 A. Correct. 10 Q. Are you an expert in the field of 11 epidemiology? 12 A. I have worked with epidemiologists 13 throughout my career, yes. 14 Q. I have, too. Does that make me an 15 expert in epidemiology? 16 MR. SLATER: Objection to the form. 17 You can answer. 18 A. I don't know. I don't know if you're 19 an expert in epidemiology. 20 Q. Do you hold yourself out as an expert 21 in the field of epidemiology? 22 A. That depends on your definition of 23 the word "expert." 24 Q. Do you agree that epidemiology is the 25 study of the distribution and determinants of a</p>
<p style="text-align: right;">Page 47</p> <p>1 of that study, correct? 2 A. Yes. 3 Q. And I think it was an animal study 4 involving rats; is that right? 5 A. Yes. 6 Q. Have you ever been involved in your 7 career in any federally-funded research projects 8 involving the carcinogenicity of NDEA? 9 A. Not specifically. 10 Q. Have you ever been involved in any 11 research projects that focused on the human body's 12 metabolism of NDEA? 13 A. Human NDMA? No, not directly. 14 Q. Have you ever been involved in any 15 research projects that focused on the human body's 16 metabolism of NDEA? 17 A. Not directly, no. 18 Q. Have you ever been involved in any 19 research projects devoted to analyzing the 20 mechanisms of action of cancer induction from 21 NDMA? 22 A. Yes. 23 Q. Would that be the same study that you 24 told me about before, the rat comparison to NNK? 25 A. That was one, yes.</p>	<p style="text-align: right;">Page 49</p> <p>1 disease in a population? 2 A. Yes. 3 Q. Do you have a degree in epidemiology? 4 A. No. 5 Q. Are you Board Certified in the field 6 of epidemiology? 7 A. No. 8 Q. Are you a pharmacoepidemiologist? 9 A. Pardon me? 10 Q. Are you a pharmacoepidemiologist? 11 A. No. 12 Q. Do you have a degree in pharmacology? 13 A. No. 14 Q. Do you agree that pharmacology is the 15 study of effects of drugs on a population? 16 A. Yes. 17 Q. Have you ever been trained or 18 employed as a clinical pharmacologist? 19 A. No. 20 Q. Are you a molecular biologist? 21 A. No. 22 Q. On your CV and also in response to 23 one of my earlier questions, you mentioned you 24 were affiliated for a time with the American 25 Health Foundation.</p>

<p style="text-align: right;">Page 50</p> <p>1 Is that right?</p> <p>2 A. I worked there for 23 years.</p> <p>3 Q. That was before you moved to the</p> <p>4 University of Minnesota, right?</p> <p>5 A. Correct.</p> <p>6 Q. Why did you leave the American Health</p> <p>7 Foundation?</p> <p>8 A. I was concerned about the future of</p> <p>9 the foundation and also I had a very nice offer</p> <p>10 from the University of Minnesota.</p> <p>11 Q. Nice offer from who?</p> <p>12 A. The University of Minnesota.</p> <p>13 Q. I'm sorry. Sometimes I don't hear</p> <p>14 great and sometimes with the computer your voice</p> <p>15 trails off a little bit, Doctor. If I ask you to</p> <p>16 repeat yourself, it's just because I couldn't hear</p> <p>17 the answer.</p> <p>18 Okay?</p> <p>19 A. Okay. Sure.</p> <p>20 The offer was from the University of</p> <p>21 Minnesota. The cancer center in particular.</p> <p>22 Q. Understood.</p> <p>23 When you were at the American Health</p> <p>24 Foundation, according to your CV, you held the</p> <p>25 title of Director of Research for over nine years;</p>	<p style="text-align: right;">Page 52</p> <p>1 for -- also responsible for funding their own</p> <p>2 research through grants and contracts mostly from</p> <p>3 the National Cancer Institute.</p> <p>4 Q. To whom did you report in your role</p> <p>5 as Director of Research when you were at the</p> <p>6 American Health Foundation?</p> <p>7 A. To Ernst Wynder, president and</p> <p>8 founder of the foundation.</p> <p>9 Q. At some point in time, the American</p> <p>10 Health Foundation changed its name to the</p> <p>11 Institute for Cancer Prevention, right?</p> <p>12 A. That was just The Institute. So the</p> <p>13 foundation included two branches. There was a</p> <p>14 branch in New York City, which focused on</p> <p>15 epidemiology. That was Dr. Wynder's specialty.</p> <p>16 You may be aware that he was the first to -- in</p> <p>17 this country -- to establish the relationship</p> <p>18 between smoking and lung cancer.</p> <p>19 Then there was The Institute, which</p> <p>20 was in Westchester County, which was the basic</p> <p>21 research, the laboratory research part of the</p> <p>22 foundation. My role was Director of Research of</p> <p>23 the laboratory part of the foundation.</p> <p>24 Q. I understand.</p> <p>25 The foundation, though, changed its</p>
<p style="text-align: right;">Page 51</p> <p>1 is that right?</p> <p>2 A. Yes.</p> <p>3 Q. Were you in charge of all the</p> <p>4 foundation's research activities during that</p> <p>5 nine-year period?</p> <p>6 A. That depends what you mean by "in</p> <p>7 charge of." I was responsible for overseeing and</p> <p>8 coordinating the research. It was up to the</p> <p>9 individual investigators to get the research</p> <p>10 funded. My role was to bring people together to</p> <p>11 look for opportunities for interdisciplinary</p> <p>12 collaboration and also to write the cancer center</p> <p>13 grant application from the foundation to the</p> <p>14 National Cancer Institute.</p> <p>15 Q. The vast majority of the funding of</p> <p>16 the American Health Foundation came from federal</p> <p>17 grants and contracts awarded through NCI, correct?</p> <p>18 A. Correct.</p> <p>19 Q. So you would have to write the grant</p> <p>20 applications to outline the scientific basis for</p> <p>21 the research that you wanted to conduct so that</p> <p>22 you could get those federal funds into the</p> <p>23 facility to do that work?</p> <p>24 A. Yes. That's true, but each</p> <p>25 individual principal investigator was responsible</p>	<p style="text-align: right;">Page 53</p> <p>1 name to the Institute for Cancer Prevention,</p> <p>2 right?</p> <p>3 A. No. The foundation never changed its</p> <p>4 name. It's the Naylor Dana Institute, which is</p> <p>5 the basic research institute. It changed its name</p> <p>6 to Institute for Cancer Prevention. That was</p> <p>7 after I left.</p> <p>8 Q. Where is the health foundation today?</p> <p>9 A. It went out of business in the late</p> <p>10 90s.</p> <p>11 Q. It's out of business just as the IFC</p> <p>12 is out of business, right?</p> <p>13 A. Yes.</p> <p>14 Q. They filed for bankruptcy, right?</p> <p>15 A. I believe. Something like that. I</p> <p>16 don't really know the details.</p> <p>17 Q. Several of the leaders of that</p> <p>18 organization were indicted on federal charges,</p> <p>19 right?</p> <p>20 A. There were some problems, yes. This</p> <p>21 was all after I left. Well after I left.</p> <p>22 Q. The leaders of the American Health</p> <p>23 Foundation and IFCP were indicted on charges of</p> <p>24 improperly diverting and misusing federal funds</p> <p>25 for cancer research, right?</p>

<p style="text-align: right;">Page 54</p> <p>1 A. Something like that, yes.</p> <p>2 Q. Several of the members of the</p> <p>3 management group, including the CFO, pled guilty</p> <p>4 to those charges, right?</p> <p>5 A. I guess so.</p> <p>6 Q. Were any charges ever brought against</p> <p>7 you?</p> <p>8 A. No.</p> <p>9 Q. Were you ever interviewed or</p> <p>10 investigated by the FBI in connection with AHF and</p> <p>11 IFCP's misuse of federal funds?</p> <p>12 A. No.</p> <p>13 Q. In addition to the criminal matters,</p> <p>14 there were also a lot of civil charges that were</p> <p>15 brought by the United States Department of Justice</p> <p>16 against your old employer and its employees,</p> <p>17 right?</p> <p>18 A. I really don't know anything about</p> <p>19 that.</p> <p>20 Q. Were any charges -- civil charges --</p> <p>21 brought against you from your work at --</p> <p>22 A. No.</p> <p>23 Q. -- AHF?</p> <p>24 A. No.</p> <p>25 Q. Isn't it true that many of the</p>	<p style="text-align: right;">Page 56</p> <p>1 Is this an argument now that you'd</p> <p>2 like to start with Dr. Hecht or do you have</p> <p>3 another question?</p> <p>4 MR. TRISCHLER: I thought I did ask a</p> <p>5 question, Adam.</p> <p>6 MR. SLATER: I took it as</p> <p>7 argumentative and I object to it.</p> <p>8 You can answer, but I'm sure he's</p> <p>9 going to -- Mr. Trischler will start asking</p> <p>10 direct questions instead of what just</p> <p>11 happened.</p> <p>12 A. What was the question again?</p> <p>13 Q. There were federal investigations,</p> <p>14 federal indictments and federal charges of fraud</p> <p>15 against AHF, IFCP and its employees for misuse of</p> <p>16 federal funds.</p> <p>17 You are aware of that; true?</p> <p>18 A. I heard about it.</p> <p>19 Q. And at the time that you were</p> <p>20 Director of Research, isn't it true that AHF</p> <p>21 settled a federal lawsuit by paying the government</p> <p>22 millions of dollars to replace and reimburse the</p> <p>23 government for misuse of federal grant monies?</p> <p>24 A. I don't know. I don't think that</p> <p>25 happened when I was there. It may have. I don't</p>
<p style="text-align: right;">Page 55</p> <p>1 allegations that were brought by the federal</p> <p>2 government involving misuse of funds at IFCP and</p> <p>3 AHF predate your departure from the organization?</p> <p>4 A. I really don't know.</p> <p>5 Q. You don't remember hearing anything</p> <p>6 about any of that while you were there?</p> <p>7 A. No.</p> <p>8 Q. You said earlier that you were</p> <p>9 concerned about the future of the organization,</p> <p>10 which is one of the reasons why you left.</p> <p>11 A. Yes.</p> <p>12 Q. Did your concern have something to do</p> <p>13 with the federal charges and federal</p> <p>14 investigations that were going on?</p> <p>15 A. Not at all.</p> <p>16 Q. Why were you concerned about the</p> <p>17 future of the organization when you were there?</p> <p>18 A. Ernst Wynder's management style</p> <p>19 about, you know, the allocation of resources</p> <p>20 within the institute. It had nothing to do with</p> <p>21 any of the things you're talking about.</p> <p>22 Q. The things I'm talking about actually</p> <p>23 happened.</p> <p>24 You know that, right?</p> <p>25 MR. SLATER: Objection.</p>	<p style="text-align: right;">Page 57</p> <p>1 know. I honestly don't know.</p> <p>2 Q. Were you ever deposed in connection</p> <p>3 with any of those lawsuits?</p> <p>4 A. No.</p> <p>5 Q. Did you ever given sworn testimony in</p> <p>6 connection with any of those lawsuits?</p> <p>7 A. No.</p> <p>8 Q. Was the scrutiny from the federal</p> <p>9 authorities and investigators anything that led to</p> <p>10 your departure from that company and your decision</p> <p>11 to head to the University of Minnesota?</p> <p>12 A. No, not at all.</p> <p>13 Q. In your report that I have marked as</p> <p>14 Exhibit 1, you indicated that you've been involved</p> <p>15 in the -- in research relating to nitrosamine</p> <p>16 since 1973.</p> <p>17 A. Correct.</p> <p>18 Q. That's true?</p> <p>19 A. Yes.</p> <p>20 Q. How many different nitrosamines have</p> <p>21 been identified by the scientific community?</p> <p>22 A. How many have been identified?</p> <p>23 Q. Yes, sir.</p> <p>24 A. Do you mean in connection with cancer</p> <p>25 or --</p>

<p style="text-align: right;">Page 58</p> <p>1 Q. No.</p> <p>2 A. -- just in general? I mean, you</p> <p>3 know, there's an infinite number of possible</p> <p>4 nitrosamines that can be synthesized and</p> <p>5 identified. The actual number that have actually</p> <p>6 been identified by chemists, it's probably in the</p> <p>7 hundreds. I don't really know that number.</p> <p>8 Q. Okay.</p> <p>9 A. They're not all -- wouldn't all be</p> <p>10 with respect to cancer research. I mean</p> <p>11 nitrosamines have been known as a class --</p> <p>12 chemical class long before they were known to be</p> <p>13 carcinogenic.</p> <p>14 Q. I appreciate all that information and</p> <p>15 I understand that there may be nitrosamines that</p> <p>16 can be synthesized that have yet to be identified.</p> <p>17 I was just asking if you know generally from your</p> <p>18 involvement in this field how many have been</p> <p>19 identified both as carcinogenic and</p> <p>20 noncarcinogenic.</p> <p>21 What you told me is that the number</p> <p>22 is in the hundreds, right?</p> <p>23 A. Yeah. As carcinogenic?</p> <p>24 Q. No. That wasn't my question.</p> <p>25 A. Okay. What's your question?</p>	<p style="text-align: right;">Page 60</p> <p>1 A. Yes.</p> <p>2 Q. Your research was fundamentally</p> <p>3 important in identifying those nitrosamines as</p> <p>4 carcinogenic, correct?</p> <p>5 A. Yes.</p> <p>6 Q. Is NNK listed as a Class 1</p> <p>7 carcinogen?</p> <p>8 A. NNK and NNN are together considered</p> <p>9 Class 1 by IARC. They're listed together because</p> <p>10 they always occur together.</p> <p>11 Q. While most of your work and research</p> <p>12 is focused on nitrosamines contained in tobacco</p> <p>13 products, is it fair to say that you've not</p> <p>14 researched all the 300 plus nitrosamines</p> <p>15 recognized by the scientific community?</p> <p>16 A. Not all of them, no.</p> <p>17 Q. Prior to your retention in this case,</p> <p>18 had you ever published any research dealing</p> <p>19 specifically with the carcinogenicity of NDEA in</p> <p>20 humans?</p> <p>21 A. I think you asked me that before.</p> <p>22 No.</p> <p>23 Q. I asked you before whether you'd done</p> <p>24 any research. This question is whether you</p> <p>25 published --</p>
<p style="text-align: right;">Page 59</p> <p>1 Q. Total number of nitrosamines that</p> <p>2 have been identified.</p> <p>3 A. Independent of any biological</p> <p>4 activity?</p> <p>5 Q. Yes.</p> <p>6 A. In all the chemical literature?</p> <p>7 Q. Yes.</p> <p>8 A. I'm guessing between 100 and 200.</p> <p>9 Q. I've seen research suggesting there's</p> <p>10 been as many as 300 nitrosamines identified.</p> <p>11 Would you dispute that?</p> <p>12 A. That's possible, sure. Nitrosamines</p> <p>13 or nitroso compounds?</p> <p>14 Q. Nitrosamines.</p> <p>15 A. You're sure of that?</p> <p>16 Q. So if we just use the number 300,</p> <p>17 while the scientific community has identified</p> <p>18 around 300 different nitrosamines, is it true that</p> <p>19 most of your research has focused on nitrosamines</p> <p>20 found in tobacco products?</p> <p>21 A. Yes.</p> <p>22 Q. For instance, you've told us here</p> <p>23 today that you continue to work on and do</p> <p>24 important research on tobacco-related nitrosamines</p> <p>25 like NNK and NNN?</p>	<p style="text-align: right;">Page 61</p> <p>1 A. No, not NDEA.</p> <p>2 Q. Your work, your published research</p> <p>3 with respect to NDEA related to a comparative</p> <p>4 evaluation of the toxicity of NDEA to NNK,</p> <p>5 correct?</p> <p>6 A. Correct.</p> <p>7 That was NDMA.</p> <p>8 Q. If I misspoke, I apologize. Yes.</p> <p>9 In that comparative analysis --</p> <p>10 A. Right.</p> <p>11 Q. -- toxicity was an animal study done</p> <p>12 in rats, right?</p> <p>13 A. Correct.</p> <p>14 Q. Have you ever in the course of your</p> <p>15 career prior to your retention in this case</p> <p>16 published any research dealing with the</p> <p>17 carcinogenicity of NDMA in humans?</p> <p>18 A. No.</p> <p>19 Q. Prior to your retention in this case,</p> <p>20 had you ever published any research on human DNA</p> <p>21 repair capacity when exposed to NDMA or NDEA?</p> <p>22 A. No.</p> <p>23 Q. Prior to your retention in this case,</p> <p>24 have you ever published any peer-reviewed research</p> <p>25 dealing directly with the level of the reactivity</p>

<p style="text-align: right;">Page 62</p> <p>1 stability and DNA binding of NDMA or NDEA when 2 exposed to -- as a result of human exposure to 3 those chemicals? 4 A. No. 5 Q. Prior to this case, have you ever 6 studied and published on the efficiency of human 7 metabolic enzymes in metabolizing and eliminating 8 NDMA or NDEA? 9 MR. SLATER: Objection. 10 You can answer. 11 A. No. 12 Q. Did you answer, sir? If you did, I 13 didn't hear. 14 A. The answer is no. 15 Q. Are you a pharmacokineticist? 16 A. No. 17 Q. Do you recognize pharmacokinetics as 18 the discipline that's involved in studying the 19 absorption, delivery, metabolism and elimination 20 of substances from the body? 21 A. Yes. 22 Q. You've never been trained in that 23 discipline, correct? 24 MR. SLATER: Objection. 25 A. Correct.</p>	<p style="text-align: right;">Page 64</p> <p>1 and DNA adducts -- adducts, A-D-D-U-C-T-S, for the 2 court reporter -- of PAH and aldehydes. 3 Did I pronounce that correctly? 4 A. Yes. 5 Q. What is PAH and aldehydes? What are 6 they? 7 A. Polycyclic aromatic hydrocarbons. 8 Those are carcinogens present in the environment 9 and in tobacco smoke that form as a result of 10 incomplete combustion of organic matter. The best 11 known of which is benzoapyrene. 12 Aldehydes are a class of chemical 13 compounds. The best known are formaldehyde and 14 acid aldehyde and acrolein that are formed in 15 human metabolism of alcohol and they're also 16 humans are exposed through the general environment 17 and tobacco smoke, as well as endogenous roots. 18 Q. Okay. 19 Then the fourth of five things that 20 you list under your contributions to science is 21 chemo prevention of cancer and that's -- that 22 involves studying things that can help prevent the 23 carcinogenic effect of exposures, correct? 24 A. Yes. 25 Q. Like the RO1 study involving the</p>
<p style="text-align: right;">Page 63</p> <p>1 Q. You've never published any research 2 on the pharmacokinetics of NDMA or NDEA; is that 3 true? 4 A. Yes. 5 Q. The CV that you provided to us which 6 we marked as Exhibit 2 lists some major 7 contributions to science that begin on page six. 8 It's actually under the title "Selected 9 Contributions to Science." 10 Are you familiar with that -- 11 A. Yes. 12 Q. -- in your CV? 13 A. Yes. 14 Q. The first one that you list there is 15 basically the study of tobacco-specific 16 nitrosamines and the identification of NNN and 17 NNK, which we talked about, correct? 18 A. Yes. 19 Q. Then you then list the -- number two 20 as being the application of tobacco carcinogen and 21 toxic and biomarkers in clinical and 22 epidemiological studies, correct? 23 A. Correct. 24 Q. The third thing you list under your 25 significant contributions to science is metabolism</p>	<p style="text-align: right;">Page 65</p> <p>1 salad we talked about? 2 A. Watercress, yes. 3 Q. Learn something new every day. I 4 never knew what watercress was. 5 A. Now you know. 6 Q. Number five is expertise in tobacco 7 carcinogenesis, correct? 8 A. Yes. 9 Q. In going through your CV and listing, 10 you know, what your major scientific contributions 11 have been during your long career, you don't 12 mention anything specifically related to NDEA, 13 true? 14 A. Correct. 15 Q. You don't mention anything 16 specifically related to NDMA, correct? 17 A. Correct. 18 Q. Do you hold yourself out as an expert 19 in toxicology? 20 A. No. I'm not a toxicologist. 21 Q. Are you a member of the Society of 22 Toxicology? 23 A. No. I don't think I paid my dues. I 24 was a member, but I'm not now. 25 MR. TRISCHLER: I'm not sure what</p>

<p style="text-align: right;">Page 66</p> <p>1 that noise is.</p> <p>2 Can everyone mute their line, please?</p> <p>3 MR. SLATER: Someone is certainly off</p> <p>4 mute.</p> <p>5 THE VIDEOGRAPHER: I just muted them</p> <p>6 for you guys.</p> <p>7 MR. TRISCHLER: Sorry about that,</p> <p>8 Doctor.</p> <p>9 Q. Prior to your retention in this case,</p> <p>10 did you ever conduct a toxicological evaluation of</p> <p>11 human health risks from exposure to NDMA?</p> <p>12 A. No.</p> <p>13 Q. Prior to your retention in this case,</p> <p>14 had you ever conducted a toxicological evaluation</p> <p>15 of human health risk from exposure to NDEA?</p> <p>16 A. No, but I'm not sure exactly what you</p> <p>17 mean by toxicological evaluation. I mean, I've</p> <p>18 served on committees -- I do serve on a committee</p> <p>19 presently looking at nitrosamines and food and</p> <p>20 I've been on an FDA panel which talked about</p> <p>21 nitrosamine contamination of the drugs, so I'm not</p> <p>22 sure exactly what you mean by the question.</p> <p>23 Q. Let me see if I could clear it up</p> <p>24 then.</p> <p>25 Have you ever published in the</p>	<p style="text-align: right;">Page 68</p> <p>1 "Comparative Tumorigenicity of DNA Methylation in</p> <p>2 F344 Rats by MethylNitrosamino Butanone and</p> <p>3 Nitrosodimethylamine."</p> <p>4 How did I do in the pronunciations?</p> <p>5 A. Pretty bad.</p> <p>6 Q. Surprising.</p> <p>7 Do you have that paper in front of</p> <p>8 you or do you need it? If not, I could have it</p> <p>9 put up on the screen?</p> <p>10 A. I don't have it in front of me.</p> <p>11 MR. TRISCHLER: Bill, can you put it</p> <p>12 up?</p> <p>13 THE VIDEOGRAPHER: Sure.</p> <p>14 What is the name of the file? I</p> <p>15 don't see one that started with what you had</p> <p>16 announced.</p> <p>17 MR. TRISCHLER: I think the file</p> <p>18 would be Comparative Tumorigenicity --</p> <p>19 THE VIDEOGRAPHER: I'm not seeing --</p> <p>20 I'm going to scroll through. I'm going to</p> <p>21 see if it's maybe labeled something else.</p> <p>22 Yes, got it. One moment.</p> <p>23 Q. So I put up as Exhibit 4 at least the</p> <p>24 first page of your paper that we've been talking</p> <p>25 about, Dr. Hecht.</p>
<p style="text-align: right;">Page 67</p> <p>1 peer-reviewed scientific literature any data that</p> <p>2 would provide a toxicological assessment of human</p> <p>3 health risk from exposure to NDMA?</p> <p>4 A. Well, we published work that could</p> <p>5 contribute to that. As far as an overall</p> <p>6 toxicological evaluation, no.</p> <p>7 Q. Have you ever published an overall</p> <p>8 toxicological evaluation of NDEA?</p> <p>9 A. No.</p> <p>10 Q. You list in your bibliography about</p> <p>11 618 entries that you have been responsible for.</p> <p>12 Do you recall that?</p> <p>13 A. Yes.</p> <p>14 Q. I know that one dealt specifically</p> <p>15 with NDMA because we've already talked a little</p> <p>16 bit about it. That would be the comparative study</p> <p>17 between NDMA and NNK, right?</p> <p>18 A. Yes.</p> <p>19 MR. TRISCHLER: Why don't we just go</p> <p>20 ahead and have that -- since we've been</p> <p>21 referring to it -- that paper marked. I</p> <p>22 think we'll mark it Exhibit 4 we're up to.</p> <p>23 (Whereupon, Exhibit 4 was marked for</p> <p>24 identification.)</p> <p>25 Q. It's entitled, for the record,</p>	<p style="text-align: right;">Page 69</p> <p>1 To go through this efficiently, I'll</p> <p>2 just ask questions and if you need to review or</p> <p>3 consult any part of your paper to answer them,</p> <p>4 please let me know that and we can take as much</p> <p>5 time as you need to read the document or to review</p> <p>6 a section of it.</p> <p>7 Okay?</p> <p>8 A. Okay.</p> <p>9 Q. In this paper, as we've already</p> <p>10 talked about, the purpose of it was to compare the</p> <p>11 toxicity and potency of NNK to NDMA, right?</p> <p>12 A. The carcinogenicity, yes. Not</p> <p>13 necessarily the toxicity.</p> <p>14 Q. Okay. Understood.</p> <p>15 As I understand it, a group of 30</p> <p>16 rats was given IV doses of NNK for 20 weeks; is</p> <p>17 that right?</p> <p>18 A. IV?</p> <p>19 Q. Yes, that's what I said.</p> <p>20 A. Sub Q I thought it was.</p> <p>21 Q. Okay. There's a section marked</p> <p>22 "Bioassay" on the first page there. Can you blow</p> <p>23 that up for the doctor? Maybe I misread it,</p> <p>24 but --</p> <p>25 A. SC. Subq. Subcutaneous injection,</p>

<p style="text-align: right;">Page 70</p> <p>1 not IV.</p> <p>2 Q. Okay.</p> <p>3 So we had a group of 30 rats that</p> <p>4 were given subcutaneous injection doses of NNK for</p> <p>5 20 weeks, right?</p> <p>6 A. Yes.</p> <p>7 Q. Another group of 30 that were given</p> <p>8 NNK for the same period of time?</p> <p>9 A. Correct.</p> <p>10 Q. By the way, 20 weeks is about 20% of</p> <p>11 the life expectancy of a rat, right?</p> <p>12 A. Twenty weeks, something like that.</p> <p>13 MR. SLATER: Before we continue, can</p> <p>14 you please put that document in the folder so</p> <p>15 it would be accessible to everybody?</p> <p>16 MR. TRISCHLER: Sure.</p> <p>17 THE VIDEOGRAPHER: It should be in</p> <p>18 there. Are you not seeing it? I would just</p> <p>19 suggest --</p> <p>20 MR. SLATER: Not there.</p> <p>21 MR. TRISCHLER: All the exhibits</p> <p>22 should be placed in the chat or in a folder</p> <p>23 for everyone's --</p> <p>24 THE VIDEOGRAPHER: Just try to</p> <p>25 refresh the page.</p>	<p style="text-align: right;">Page 72</p> <p>1 if I could do it in my head. So 0.3 millimoles</p> <p>2 per kilogram, so a 150-pound person is about</p> <p>3 70 kilograms. 0.3 millimoles per 70 kilograms</p> <p>4 would be -- I don't know. I can't do it in my</p> <p>5 head. I'm sorry.</p> <p>6 Q. That's fair. I couldn't do it</p> <p>7 either.</p> <p>8 I'll represent to you I did run</p> <p>9 this --</p> <p>10 A. It's significantly higher than the</p> <p>11 human dose, if that's what you're getting to. We</p> <p>12 don't have to waste time going through -- I mean,</p> <p>13 the purpose of this experiment was to compare NNK</p> <p>14 and DMN -- NDMA.</p> <p>15 Q. Understood.</p> <p>16 A. The dose -- the dose is far higher</p> <p>17 than a human dose. If you want to get to human</p> <p>18 dose, you have to look at the Peto study.</p> <p>19 Q. We'll get there.</p> <p>20 What we can agree upon is that in</p> <p>21 this particular study that the dose administered</p> <p>22 to rats was on order of magnitude greater than the</p> <p>23 nitrosamine levels seen in valsartan-containing</p> <p>24 medications, correct?</p> <p>25 A. Yes, absolutely.</p>
<p style="text-align: right;">Page 71</p> <p>1 MR. SLATER: It's in there now.</p> <p>2 THE VIDEOGRAPHER: Great.</p> <p>3 MR. SLATER: Sorry about that.</p> <p>4 MR. TRISCHLER: That's all right.</p> <p>5 BY MR. TRISCHLER:</p> <p>6 Q. So dosing a rat for about 20 weeks or</p> <p>7 20% of its life expectancy would be the equivalent</p> <p>8 of dosing a human for about 15 years, correct?</p> <p>9 A. Yeah.</p> <p>10 Q. And you understand that when we talk</p> <p>11 about this case for just a moment, you understand</p> <p>12 that there's no plaintiff in this litigation who</p> <p>13 ingested valsartan-containing medications</p> <p>14 containing nitrosamines for 15 years, right?</p> <p>15 A. Correct.</p> <p>16 Q. And the total dose that was given to</p> <p>17 these rats in your study was listed as 0.33</p> <p>18 mmol/kilogram.</p> <p>19 Is that right?</p> <p>20 A. Yes.</p> <p>21 Q. Can you equate that to a human dose</p> <p>22 for a 150-pound individual?</p> <p>23 A. You want me to do that now?</p> <p>24 Q. Are you able to?</p> <p>25 A. I'm able to, yeah, but I don't know</p>	<p style="text-align: right;">Page 73</p> <p>1 Q. And there is a formula for converting</p> <p>2 these doses to a human equivalent dose, correct?</p> <p>3 A. Yes.</p> <p>4 Q. I think we can agree that formula is</p> <p>5 not easy to do in one's head, but I've done the</p> <p>6 math and I'll represent to you that the human</p> <p>7 equivalent dose in this study would equate to</p> <p>8 about 336 million nanograms.</p> <p>9 Does that sound about right?</p> <p>10 A. I'll take your word for it. But I</p> <p>11 mean this study was not designed to look at human</p> <p>12 doses at all.</p> <p>13 Q. It wasn't designed to look --</p> <p>14 A. It was designed to compare NNK and</p> <p>15 NDMA carcinogenicity and metabolism using the</p> <p>16 doses of NNK that we knew induced a certain</p> <p>17 percentage of lung tumors.</p> <p>18 Q. This study that we marked as Exhibit</p> <p>19 4 was not designed to look at issues of human</p> <p>20 carcinogenicity of NDMA, correct?</p> <p>21 A. That's a very broad statement. It</p> <p>22 wasn't designed to replicate the human dose of</p> <p>23 NDMA. Not at all.</p> <p>24 Q. Okay.</p> <p>25 The point is that the animals in your</p>

<p style="text-align: right;">Page 74</p> <p>1 study were administered nitrosamines in far 2 greater quantities and over a greater period of 3 their life span than any plaintiff in this 4 litigation. 5 Can we agree on that? 6 A. That's the point you're making, yes. 7 Q. And is the point I'm making accurate? 8 A. Yes. 9 Q. After a long period of exposure at 10 doses far higher than what's contained in any of 11 the valsartan-containing medications, what your 12 study showed was a development of tumors in six of 13 the 30 rats that were administered these high, 14 high doses of NDMA, right? 15 A. Yes. 16 MR. SLATER: Objection. 17 Lack of foundation and multiple other 18 objections. 19 You can answer. 20 A. Yes. 21 Q. In the conclusion of your study was 22 that NNK is more potent than NDMA? 23 A. That was the conclusion. 24 Q. And we know today that NNK and NNN 25 are Class 1 known carcinogens, right?</p>	<p style="text-align: right;">Page 76</p> <p>1 the last year and I haven't heard anyone say 2 we need to stop because of the media cut off. 3 There's a first for everything. We want to 4 use as much time as we can and keep going. 5 MR. TRISCHLER: Bill, you could take 6 down Exhibit 4. 7 BY MR. TRISCHLER: 8 Q. So before we started talking 9 specifically about your paper that we marked as 10 Exhibit 4, Dr. Hecht, I was asking about your 11 bibliography. 12 Those 618 entries that are on it, do 13 any of them deal specifically with the 14 carcinogenicity of NDEA? 15 A. No. 16 Q. Other than the comparative paper that 17 we marked as Exhibit 4, do any of those 618 papers 18 that you list on your bibliography deal with the 19 carcinogenicity of NDMA in any way? 20 A. No. 21 Q. You also list on your -- as part of 22 your CV that we marked as Exhibit 2 some 280 23 chapters, articles and what's called other papers. 24 Are you familiar with that section of 25 your CV, sir?</p>
<p style="text-align: right;">Page 75</p> <p>1 A. Yes. 2 Q. NDMA is not? 3 A. Correct. It's 2A. 4 THE VIDEOGRAPHER: Counsel, I just 5 want to let you know I have about ten minutes 6 left on this media before I need to do a 7 quick break to change. 8 MR. SLATER: Why is that? Aren't you 9 just recording with the Zoom? 10 THE VIDEOGRAPHER: We run an hour and 11 a half. It's a Veritext standard. 12 MR. SLATER: Well, is it 13 technological issue or is it just a Veritext 14 standard? 15 THE VIDEOGRAPHER: Well, you know, it 16 necessitates the issue that if we go two 17 hours and it crashes, we lose two hours as 18 opposed -- 19 MR. SLATER: Okay. I got it. It's a 20 Veritext issue. Thank you. 21 You can continue. 22 MR. TRISCHLER: Adam, would you want 23 to stop now or go -- 24 MR. SLATER: I've never heard of any 25 such thing. I've been in 100 depositions in</p>	<p style="text-align: right;">Page 77</p> <p>1 A. Yes. 2 Q. Do any of those 280 chapters, 3 articles or other papers deal specifically with 4 the carcinogenicity of NDMA? 5 A. Yes. 6 Q. Can you tell me which ones? 7 A. No. I've written a number of 8 chapters for books dealing with the metabolic 9 activation or metabolism usually of nitrosamines 10 and NDMA metabolism is kind of the classic 11 example. So in a number of those chapters, NDMA 12 will have been used as an example of the metabolic 13 activation process by which nitrosamines are 14 metabolized and bind to DNA leading to miscoding 15 and activation of ANCA genes and cancer. 16 Q. You've told me -- 17 A. That's covered in a number of those 18 book chapters. 19 Q. You told me that you have your report 20 in front of you in a hard copy form and I know the 21 bibliography is part of the report. 22 What I'd ask you to do is go to the 23 section marked "Chapters, Invited Articles, Books 24 and Other Papers" and look at it and identify for 25 me a few of the places that I can go to read what</p>

<p style="text-align: right;">Page 78</p> <p>1 you've written about NDMA. 2 A. Okay. Well, I don't have the hard 3 copy of the bibliography in front of me, so I'll 4 have to pull it up on my computer. Then I can go 5 through and then I can tell you. That'll take a 6 few minutes. 7 MR. TRISCHLER: All right. We need 8 to take a break for the videographer, so 9 let's take a break. If you don't mind 10 looking at that -- 11 MR. SLATER: No, Clem. We're not 12 going to do that during the break. I don't 13 want to him doing work that should be on the 14 record during a break. 15 MR. TRISCHLER: Well, we could do 16 it when we come back then, Adam -- 17 MR. SLATER: Yeah, I just want him to 18 be able to take a break, stretch his legs and 19 all. 20 MR. TRISCHLER: That's fine. 21 Whatever you want to do. Let's take a break, 22 we'll get the medium up and running and when 23 you're ready to come back, we will pick up 24 with this. 25 MR. SLATER: Let's take no more than</p>	<p style="text-align: right;">Page 80</p> <p>1 I have to -- that'll take some more time. 2 Q. You could do it now. 3 A. Okay. 4 (Witness reviews document) 5 Q. Dr. Hecht, may I make a suggestion 6 while you're doing this? 7 A. Yes. 8 Q. If you have located three or four 9 that are responsive, that's all I need. I'm not 10 looking for you to tell me every single one. Just 11 a few. 12 A. Okay. So the question is whether 13 they specifically have dimethylnitrosamine as 14 opposed to nitrosamines in general, correct? 15 Q. Correct. 16 A. That's the problem I'm having because 17 I don't remember whether I specifically talked 18 about dimethylnitrosamine, but -- so there's one 19 paper in Environmental and Occupational Medicine, 20 Third Edition, 1998. It's a chapter on 21 N-nitrosamines. 22 Q. What number on the bibliography, sir? 23 A. It's 149 under the "Chapters" 24 section. One forty-nine. That would be an 25 example.</p>
<p style="text-align: right;">Page 79</p> <p>1 ten minutes and come back. 2 THE VIDEOGRAPHER: The time is 10:37. 3 We're going off the video record. 4 This ends media one. 5 (Recess taken) 6 THE VIDEOGRAPHER: The time is now 7 10:49. 8 This begins media two. 9 You may proceed. 10 Q. Welcome back, Dr. Hecht. 11 Before we took a break, we were 12 talking about the section of your bibliography 13 that's part of Exhibit 2 entitled "Chapters, 14 Invited Articles, Books and Other Papers." 15 Do you remember that? 16 A. Yes. 17 Q. Have you been able to find that 18 section of your bibliography on your desktop 19 there? 20 A. Yes. 21 Q. I had asked if you would be kind 22 enough to peruse that section and just identify 23 for me a couple of the publications that you were 24 a part of that discuss NDMA. 25 A. Right. I couldn't quite do that, so</p>	<p style="text-align: right;">Page 81</p> <p>1 Q. I'll accept that. You don't need to 2 look at any further. 3 A. All right. 4 Q. So let me ask sort of the same 5 question, but this time related to NDEA. 6 Do any of the chapters, invited 7 articles, books or other papers listed in your CV 8 that we've marked as Exhibit 2 specifically deal 9 with or discuss the carcinogenicity after NDEA? 10 A. No, I don't believe so. 11 Q. Are you familiar with the term 12 "threshold dose" as used in the field of 13 toxicology? 14 A. Yes. 15 Q. What do you understand that term to 16 mean, sir? 17 A. A dose below which there would be no 18 effect. 19 Q. By no effect, you mean no toxicity or 20 harm is -- 21 A. Right. Whatever the end point is. 22 Q. In your career, have you ever done 23 any original research to evaluate or establish a 24 threshold dose for NDMA in humans? 25 A. No.</p>

<p style="text-align: right;">Page 82</p> <p>1 Q. Have you ever done any research to 2 evaluate a threshold dose for NDEA in humans? 3 A. No. 4 Q. Let me ask a little bit about 5 valsartan if I can. 6 Do you understand that valsartan 7 falls into a class of drugs known as angiotensin 8 receptor blockers or ARBs? 9 A. Yes. 10 Q. Do you understand that ARBs are used 11 in the treatment and management of hypertension? 12 A. Yes. 13 Q. Hypertension and heart disease are 14 the number one cause of death of adults in 15 America; true? 16 A. Yes. 17 Q. Do you agree that 18 valsartan-containing medications have proven to be 19 effective in the treatment and management of this 20 deadly condition? 21 A. Yes. 22 Q. Do you agree that 23 valsartan-containing medications are an important 24 tool for clinicians to manage and treat this 25 deadly disease?</p>	<p style="text-align: right;">Page 84</p> <p>1 I don't think it's appropriate to ask 2 an expert, whatever the question is about, 3 about their own personal health history. 4 MR. TRISCHLER: Only reason I ask, 5 Adam, is if he could be a potential 6 plaintiff, it goes to bias. If he's used 7 these medications, it's certainly relevant. 8 MR. SLATER: That's why you're asking 9 the question? To find out if there's a bias 10 issue? 11 MR. TRISCHLER: To find out if he's 12 used the medications that he's claiming -- 13 MR. SLATER: I'll let Dr. Hecht -- 14 MR. TRISCHLER: If he has a potential 15 claim, I think it's relevant. 16 MR. SLATER: All right. 17 I'll allow Dr. Hecht to answer one 18 question of whether he's used valsartan. 19 A. No, I haven't. 20 Q. Can we agree that hypertension is a 21 major health problem? 22 A. Yes. 23 Q. Are you aware that the CDC is 24 estimating that 45% of adult Americans suffer from 25 hypertension?</p>
<p style="text-align: right;">Page 83</p> <p>1 MR. SLATER: Objection. 2 You can answer. 3 A. Yes. 4 Q. Do you intend to offer any opinions 5 asserting that valsartan is not effective in 6 treating hypertension? 7 A. No. 8 Q. Do you intend to offer any opinion 9 that the small amounts of nitrosamine impurities 10 found in certain valsartan-containing medications 11 compromised, limited or reduced the medication's 12 effectiveness in controlling blood pressure? 13 MR. SLATER: Objection to the form. 14 A. No. 15 Q. You personally do not treat heart 16 disease, correct? 17 A. Correct. 18 Q. You're not an expert in the 19 diagnosis, treatment, management of this 20 condition; fair to say? 21 A. Correct. 22 Q. Have you ever been prescribed 23 valsartan-containing medications? 24 MR. SLATER: Objection. 25 Don't answer the question.</p>	<p style="text-align: right;">Page 85</p> <p>1 MR. SLATER: Objection to all these 2 statistical proffers. 3 You can answer. 4 A. I didn't know that number offhand, 5 but, you know, I'll take your word for it. 6 Q. Does hypertension cause cancer? 7 A. No. 8 Q. Is hypertension is risk factor for 9 cancer? 10 A. No. 11 Q. As someone who is -- 12 A. It's not a known risk factor. 13 Q. Are you aware of whether or not there 14 are peer reviewed -- strike that. 15 Are you aware as to whether or not 16 there is peer-reviewed literature that's been 17 published in the medical community noting a 18 statistically significant association between 19 hypertension and cancer? 20 A. I'm not aware of it. I may have seen 21 it. I can't think of it right now. 22 Q. As part of your work in this case, 23 did you do a literature search to determine 24 whether or not there was peer-reviewed literature 25 discussing, noting or observing a statistically</p>

<p style="text-align: right;">Page 86</p> <p>1 significant observation between hypertension and 2 cancer? 3 A. No, I did not. 4 Q. Have you ever done such a literature 5 search? 6 A. Not recently. 7 Q. Can we agree that cancer causation is 8 multifactorial? 9 A. Yes. 10 Q. I think in going through your CV one 11 of the things I observed in connection with your 12 work as a professor or research that you've done, 13 much of it is focused on cancer prevention, 14 correct? 15 A. Correct. 16 Q. As someone who is focused on cancer 17 prevention, one of the things that we've been 18 taught is that good health and good diet can go a 19 long way to reducing an individual's risk factor 20 for developing cancer, correct? 21 A. Yes. 22 Q. While we know, based on the research 23 that's been done in the past few decades, there 24 are things we could do to reduce our risk factor 25 to cancer, we still don't know what causes cancer.</p>	<p style="text-align: right;">Page 88</p> <p>1 a statistically significant increased risk of 2 kidney, colorectal, breast and other cancers in 3 patients with hypertension? 4 MR. SLATER: Objection. 5 There's a massive lack of foundation 6 and relevance, but you can answer the 7 question. Plus -- I said foundation. 8 You can answer. 9 A. Not offhand. 10 Are you still there? 11 Q. Yes, I'm just thinking what I want to 12 ask you next. 13 You told me that research and work 14 that's been done over the years will tell us that 15 cancer can be caused by many different things, one 16 of them being smoking and tobacco use, right? 17 A. Yes. 18 Q. You identified obesity as a risk 19 factor that can lead to cancer, right? 20 A. Yes. 21 Q. Alcohol use can lead to cancer, 22 correct? 23 A. Yes. 24 Q. Radiation can lead to cancer? 25 A. Yes.</p>
<p style="text-align: right;">Page 87</p> <p>1 Would you agree? 2 A. Yes. 3 Q. While there's certainly no 4 guarantees, what we believe is that a good diet, 5 exercise and good health can go a long way in 6 reducing an individual's risk; true? 7 A. There's plenty of evidence, yes. 8 Q. Based on that, would you agree that 9 hypertension can and does lead to cancer? 10 MR. SLATER: Objection. 11 You can answer. 12 A. So you can construct a connection, I 13 suppose, because, you know, good health, exercise 14 will be good in preventing hypertension and also 15 preventing cancer, so ... 16 In that respect, there could be a 17 connection, sure. 18 Q. Is it fair to say that every 19 plaintiff in this litigation was at an increased 20 risk of developing cancer before they ever took a 21 single valsartan pill? 22 MR. SLATER: Objection. 23 A. I have no idea. 24 Q. Are you aware of any peer-reviewed 25 research published in the medical journals finding</p>	<p style="text-align: right;">Page 89</p> <p>1 Q. Genetics can play a role? 2 A. Yes. 3 Q. Viruses in some circumstances can 4 cause cancer? 5 A. Yes. 6 Q. Environmental -- we believe that some 7 environmental exposures can cause cancer, correct? 8 A. Yes. Yes. 9 Q. Are there other groups of causes that 10 are risk factors that we haven't talked about? 11 A. I don't know. I think you covered 12 the main ones. Sunlight, UV exposure I don't 13 think you mentioned. 14 Q. Okay. 15 Given all these potential causes of 16 cancer, are you able to look at a mutation at a 17 cellular level and say that that mutation was 18 caused by a specific exposure or condition? 19 A. That would be very difficult. 20 Q. So I'm only asking about you, whether 21 you had that ability or capability. 22 Do you have the expertise to look at 23 a given mutation and say this was caused by 24 increased nitrosamine intake as opposed to 25 genetics, as opposed to alcohol use, as opposed to</p>

<p style="text-align: right;">Page 90</p> <p>1 any other factor known to cause cancer?</p> <p>2 MR. SLATER: Objection.</p> <p>3 You can answer.</p> <p>4 A. I didn't quite hear your question.</p> <p>5 Did you say patient or mutation?</p> <p>6 Q. Mutation I said.</p> <p>7 A. Well, some mutations are quite</p> <p>8 specific. For example, those caused by UV light,</p> <p>9 you get thymidine cross links in DNA. I'm not</p> <p>10 aware if those are caused by any other agent, so</p> <p>11 there are cases of certain mutations that are</p> <p>12 quite specific.</p> <p>13 Q. Are you aware of any unique</p> <p>14 biomarkers caused by NDMA?</p> <p>15 A. No.</p> <p>16 Q. Are you aware --</p> <p>17 A. Wait. That depends what you mean by</p> <p>18 biomarkers.</p> <p>19 Q. Are you able to look at a mutation</p> <p>20 and say this mutation was caused by NDMA exposure?</p> <p>21 A. No, not a mutation.</p> <p>22 Q. Are you able to look at a mutation</p> <p>23 and say this mutation was caused by NDEA exposure?</p> <p>24 A. No.</p> <p>25 Q. So if there are no unique biomarkers</p>	<p style="text-align: right;">Page 92</p> <p>1 A. Guanine. G-U-A-N-I-N-E.</p> <p>2 No, I haven't. But that would be a</p> <p>3 possible approach, a research approach.</p> <p>4 Q. The presence of O6-methylguanine in a</p> <p>5 DNA sample is not the equivalent of a -- does not</p> <p>6 mean there's a carcinogenic tumor, correct?</p> <p>7 A. Correct. But it's one step in a</p> <p>8 well-established pathway.</p> <p>9 Q. Is the presence of O6-methylguanine</p> <p>10 specific and limited to NDMA and NDEA exposure?</p> <p>11 A. No.</p> <p>12 Q. Going back to my question, you told</p> <p>13 me that you cannot look at a biopsied tissue and</p> <p>14 make the determination that that mutation was</p> <p>15 caused by NDMA, correct?</p> <p>16 MR. SLATER: Objection.</p> <p>17 You can answer.</p> <p>18 A. In the absence of other data, but if</p> <p>19 I had DNA from that tissue and I analyzed it for</p> <p>20 O6-methylguanine and I find O6-methylguanine and</p> <p>21 the mutation is a mutation in a raised gene and I</p> <p>22 have tissue from subjects who did not use</p> <p>23 valsartan and I don't find the mutation, that</p> <p>24 would be pretty good evidence.</p> <p>25 Q. None of that work has been done in</p>
<p style="text-align: right;">Page 91</p> <p>1 for NDMA or NDEA in human tissue and given that</p> <p>2 there are multiple risk factors for cancer, are</p> <p>3 you able to state to a reasonable degree of</p> <p>4 scientific certainty that cancer causation in any</p> <p>5 of these plaintiffs in this litigation was caused</p> <p>6 by nitrosamines?</p> <p>7 MR. SLATER: Objection.</p> <p>8 You can answer.</p> <p>9 A. I wouldn't say there's no biomarker.</p> <p>10 You mentioned certain mutations. But if I find --</p> <p>11 if I'm able to obtain a DNA sample from one of the</p> <p>12 patients, for example, from their oral cells after</p> <p>13 they took a contaminated pill and analyzed the DNA</p> <p>14 in that sample and I find O6-methylguanine in that</p> <p>15 DNA, I can be reasonably sure that came from</p> <p>16 dimethylnitrosamine. So that's a biomarker.</p> <p>17 Q. Have you obtained DNA samples from</p> <p>18 any of the plaintiffs in this case?</p> <p>19 A. No.</p> <p>20 Q. Have you looked for signs of</p> <p>21 O6-methylformane in any of the DNA samples</p> <p>22 or tissue samples from any of the plaintiffs in</p> <p>23 this case?</p> <p>24 A. O6-methylguanine.</p> <p>25 Q. Guanine.</p>	<p style="text-align: right;">Page 93</p> <p>1 this case; is that right?</p> <p>2 A. As far as I know.</p> <p>3 Q. You've not done it?</p> <p>4 A. No.</p> <p>5 Q. What causes the presence of</p> <p>6 O6-methylguanine in a DNA sample?</p> <p>7 A. From the metabolism of a substance</p> <p>8 such as NDMA that leads to the formation of methyl</p> <p>9 diazohydroxide, which reacts with guanine in DNA</p> <p>10 to form O6-methylguanine.</p> <p>11 Q. My question was other than NDMA what</p> <p>12 other substances are you aware of that lead to the</p> <p>13 formation of O6-methylguanine?</p> <p>14 A. Other methylating carcinogens, NNK,</p> <p>15 methyl methane sulfonate. I don't think there's</p> <p>16 much human exposure to that. So, you know, any</p> <p>17 methyl nitroso compound.</p> <p>18 Q. I'm sorry. I didn't mean to</p> <p>19 interrupt you. Go ahead.</p> <p>20 A. I'm done.</p> <p>21 Q. Can the presence of O6-methylguanine</p> <p>22 be attributed in a DNA sample be attributed to</p> <p>23 anything other than exposure to nitrosamines?</p> <p>24 MR. SLATER: Objection.</p> <p>25 You can answer.</p>

<p style="text-align: right;">Page 94</p> <p>1 A. Yes, it could be another methylating 2 agent. Wouldn't necessarily have to be 3 nitrosamine. Methyl methane sulfonate is one of 4 the more common ones, but it's not really found in 5 the environment. 6 Q. I'm going to go into this more a 7 little later, but all of us are exposed to 8 nitrosamines every single day, correct? 9 MR. SLATER: Objection. 10 You can answer. 11 A. Many people are, yes. 12 Q. And all of us process and develop 13 nitrosamines endogenously. 14 Our body creates them, right? 15 A. Yes, to a certain extent. 16 Q. Every single day? 17 MR. SLATER: Objection. 18 A. I don't know about every single day. 19 The measurement of endogenous formation is fraught 20 with difficulties, but there is certainly the 21 evidence for endogenous formation of nitrosamines. 22 Q. By all of us? 23 A. I don't know about all of us. 24 Q. Are you aware of any research that 25 suggests there are some individuals that have the</p>	<p style="text-align: right;">Page 96</p> <p>1 DNA sample, if you were to ever do this work, you 2 would not be able to tell us whether that 3 O6-methylguanine was from nitrosamines ingested 4 exogenously or developed endogenously, would you? 5 MR. SLATER: Objection. 6 You can answer. 7 A. I could do a study that could 8 indicate that. 9 Q. You've not done such a study? 10 A. No. 11 Q. No one in the world has done such a 12 study at this point? 13 A. I don't know. 14 Q. Are you aware of any? 15 A. No. I could compare subjects who 16 took contaminated valsartan and who did not and 17 get DNA samples from those individuals and analyze 18 them for O6-methylguanine and see if there's a 19 difference. 20 Q. Okay. You could do that -- 21 A. That would be a good start. 22 Q. Great. 23 But my question was you haven't done 24 that scientific investigation, correct? 25 A. No, but I think it would be a good</p>
<p style="text-align: right;">Page 95</p> <p>1 unique ability not to endogenously create 2 nitrosamines? 3 MR. SLATER: Objection. 4 You can answer. 5 A. Not offhand. 6 Q. Right. So here's what I don't 7 understand: If all of us or virtually all of us 8 endogenously create nitrosamines, then every DNA 9 sample that you are look at is going to have 10 O6-methylguanine. 11 A. No, that's not true. 12 Q. You just said that nitrosamine 13 exposure -- strike that. 14 A. Just because you're exposed to a 15 nitrosamine doesn't mean that you'll be able to 16 necessarily metabolize it efficiently enough to 17 alkylate DNA. So you might have cases where the 18 exposure is too low or the metabolism is not that 19 efficient. It doesn't -- you can't say all. 20 Q. O6-methylguanine observed in a DNA 21 sample is caused by the metabolism of nitrosamines 22 among other things. 23 That's what you've told me, right? 24 A. Yes. 25 Q. When you find O6-methylguanine in a</p>	<p style="text-align: right;">Page 97</p> <p>1 project. You gave me an idea. 2 Q. At least I served some purpose here 3 today then. 4 I want to go back and sort of touch 5 on one of the things that I asked you at the 6 outset and that relates to the work that you have 7 done in this case. 8 I think you told me that when you 9 wrote your report that you acknowledged that 10 valsartan -- whether or not nitrosamines in 11 valsartan-containing medications were capable of 12 causing cancer is dependent on the exposure, the 13 dose and the duration. 14 Do you remember telling me that? 15 A. Mm-hmm. 16 MR. SLATER: Objection. 17 You can answer. 18 Q. You have to say "yes" or "no" for the 19 record. 20 A. Yes. 21 Q. You gave me a general overview of 22 some of the things that you did to try and answer 23 the question of whether or not the exposure to 24 nitrosamines in valsartan-containing medications 25 was capable of increasing the risk of cancer and</p>

25 (Pages 94 - 97)

<p style="text-align: right;">Page 98</p> <p>1 you said that one of the things you did was</p> <p>2 consult literature.</p> <p>3 Correct?</p> <p>4 A. Yes.</p> <p>5 Q. How did you go about deciding upon</p> <p>6 the literature that you were going to review and</p> <p>7 cite and rely upon in your report?</p> <p>8 A. From my experience and from staying</p> <p>9 up to date on the literature. It's one of the</p> <p>10 things that we do in research, follow the</p> <p>11 literature and attempt to read it all and use it</p> <p>12 our research and let it inform us as to our</p> <p>13 projects and conclusions. So, you know, it's</p> <p>14 important to follow the literature. It's</p> <p>15 something that all researchers do.</p> <p>16 Q. Understood.</p> <p>17 When you were retained by Mr. Slater</p> <p>18 back in September of 2019, did you do any or</p> <p>19 attempt to any sort of comprehensive search of the</p> <p>20 literature or did you just rely on your knowledge</p> <p>21 and efforts to stay abreast of the literature as</p> <p>22 you described it?</p> <p>23 A. Well, I looked into the valsartan</p> <p>24 literature, but mainly I relied on my knowledge of</p> <p>25 the literature.</p>	<p style="text-align: right;">Page 100</p> <p>1 refresh my memory regarding dimethylnitrosamine</p> <p>2 exposures and cancer in the literature.</p> <p>3 Q. So how do you go about refreshing</p> <p>4 your memory in that matter?</p> <p>5 A. I go to PubMed and put in the right</p> <p>6 terms.</p> <p>7 Q. What search terms did you use to run</p> <p>8 that query?</p> <p>9 A. Oh, I don't remember.</p> <p>10 Q. Do you have a list you created?</p> <p>11 A. No, I don't have a list. I know</p> <p>12 dimethylnitrosamine and cancer. You know, it</p> <p>13 would come up with probably a thousand references</p> <p>14 and then you go from there.</p> <p>15 Q. Were those the search terms you</p> <p>16 actually used or --</p> <p>17 A. No. No. I mean, it's a mix. So I</p> <p>18 relied on my knowledge that's been gained over 45</p> <p>19 years of work in this area. I've looked into the</p> <p>20 literature specifically regarding valsartan and I</p> <p>21 updated my -- refreshed my memory regarding papers</p> <p>22 looking at dimethylnitrosamine occurrence in the</p> <p>23 environment, in food, in water, etc. So I tried,</p> <p>24 you know, to cover as much as I could.</p> <p>25 Q. I'll be honest with you, Dr. Hecht.</p>
<p style="text-align: right;">Page 99</p> <p>1 Q. So if I were to --</p> <p>2 A. But I'm not an encyclopedia, you</p> <p>3 know. I could have forgotten things here and</p> <p>4 there.</p> <p>5 Q. Well, that's what -- I'm not</p> <p>6 suggesting you should be an encyclopedia.</p> <p>7 Would you agree with me that</p> <p>8 formulating a meaningful and reliable opinion on a</p> <p>9 causality of exposure to a disease requires an</p> <p>10 evaluation of the totality of the evidence?</p> <p>11 MR. SLATER: Objection.</p> <p>12 A. Yes.</p> <p>13 Q. So what I'm trying to get a feel for</p> <p>14 and what I'd like you to explain for me is how did</p> <p>15 you set out to make sure that your encyclopedic</p> <p>16 knowledge of the literature was adequate --</p> <p>17 MR. SLATER: Objection.</p> <p>18 You can answer.</p> <p>19 Q. -- before whether it needed to be</p> <p>20 supplemented by a literature review?</p> <p>21 MR. SLATER: Objection.</p> <p>22 You can answer again.</p> <p>23 A. Sure. I needed to review the</p> <p>24 available literature on valsartan, you know, the</p> <p>25 contamination with nitrosamines. I also needed to</p>	<p style="text-align: right;">Page 101</p> <p>1 I'm trying to fact check how you did your work.</p> <p>2 You said -- you told me that you would have</p> <p>3 updated your knowledge by a literature search.</p> <p>4 Are you able to show me the actual</p> <p>5 search terms you would have used?</p> <p>6 A. No.</p> <p>7 Q. Are you able to show me the -- have</p> <p>8 you retained the print out of the results from</p> <p>9 your initial PubMed searches as far as what hits</p> <p>10 you received and so forth?</p> <p>11 A. No.</p> <p>12 MR. SLATER: Objection.</p> <p>13 You can answer.</p> <p>14 Q. Do you know how many publications you</p> <p>15 pulled in on your initial search?</p> <p>16 A. No.</p> <p>17 Q. One of the things that I asked you to</p> <p>18 bring with you or to the deposition with a notice</p> <p>19 and one of the things that your counsel was kind</p> <p>20 enough to provide to me before we began were your</p> <p>21 invoices that you've generated in connection with</p> <p>22 your work in this project.</p> <p>23 Are you aware of that?</p> <p>24 A. Yes.</p> <p>25 Q. Did you provide those invoice</p>

<p style="text-align: right;">Page 102</p> <p>1 documents to counsel so that he could provide them 2 to me? 3 A. Yes. Yes. 4 MR. TRISCHLER: Can we mark those as 5 Exhibit 4? 6 THE VIDEOGRAPHER: Exhibit 4 was the 7 comparative -- 8 MR. TRISCHLER: Exhibit 5. Exhibit 9 5. 10 THE VIDEOGRAPHER: What was the name 11 of the document again that you wanted -- 12 MR. TRISCHLER: Invoices. 13 THE VIDEOGRAPHER: Okay. Great. 14 Would you like that up on the screen? 15 MR. TRISCHLER: Yes. 16 (Whereupon, Exhibit 5 was marked for 17 identification.) 18 Q. The documents related to your 19 invoices that we marked as Exhibit 5 consist of 20 four pages. What we're looking at here is the 21 first of those four pages that I have. 22 A. Yes. 23 Q. This appears to me, Dr. Hecht, to be 24 a summary of the work that you did from at least 25 September of 2019 through June of 2020, right?</p>	<p style="text-align: right;">Page 104</p> <p>1 MR. SLATER: You can go to the next 2 page, sir. 3 Can you highlight that for the 4 doctor? 5 Q. Is there any reference to your 6 literature search on this page of the billing 7 records? 8 A. Well, the updated report adding new 9 text and references, so, you know, that could have 10 involved some literature. I really don't 11 remember. 12 Q. How about the next page? 13 A. Right. There's no reference to 14 literature search there. 15 Q. How about the last page? 16 A. That's it. 17 Q. So if we look at all the invoice 18 documents that I've been provided with, what it 19 suggests is that there's only one reference to a 20 literature search and that was for an hour on 21 December of 2019. 22 Is that the extent of the literature 23 search that you -- 24 MR. SLATER: Objection. 25 Lack of foundation.</p>
<p style="text-align: right;">Page 103</p> <p>1 A. Yes. 2 Q. You would have billed for your work 3 in connection with this case based on this 4 summary, right? 5 A. Yes. 6 Q. What I'm curious about is when I read 7 this document and look at this document marked as 8 Exhibit 5, I don't see any reference to a 9 literature search being done until -- well, 10 actually in -- I stand corrected -- 12/9/19. It 11 says "Further review and literature search on 12 NDMA, one hour." 13 A. Yes. 14 Q. Is that when you would have done your 15 literature search then? 16 A. That's what it says. 17 MR. SLATER: Objection. 18 You can answer. 19 Q. And your search of the literature 20 would have taken you an hour to do? 21 A. On that particular day, yes. 22 Q. Is there any reference to any 23 literature search on any other day in your 24 records? 25 A. I don't know.</p>	<p style="text-align: right;">Page 105</p> <p>1 You can answer, Doctor. 2 A. I do literature work all the time on 3 nitrosamine. It's my part of my work. 4 Q. All right. 5 I'm talking about -- you said you 6 keep abreast of the literature. You're looking at 7 it all the time. 8 A. Yes. 9 Q. You're not an encyclopedia and so you 10 did a literature search to supplement your 11 knowledge. 12 Is that supplement the one hour we 13 see in December of 2019? 14 MR. SLATER: Objection. 15 Foundation. 16 Argumentative. 17 You can answer. 18 A. That's what it says. 19 Q. You didn't -- according to your 20 billing records, you didn't spend any other time 21 on the literature search, right? 22 MR. SLATER: Objection. 23 You can answer. 24 A. I didn't bill for it. 25 Q. Do you remember doing it?</p>

<p style="text-align: right;">Page 106</p> <p>1 A. As I said, I look at the literature 2 almost every day in one form or another, so I 3 don't necessarily bill for it. It's part of my 4 work. It's part of what I do. 5 Q. In your report that you provided to 6 us, you have footnotes, footnote references at the 7 conclusion of the report, a grand total of about 8 146, correct? 9 A. Yes. 10 Q. It looked to me like the last -- you 11 have that report in front of you, sir. 12 The last footnote, 146, is a true 13 footnote, whereas the other 145 are citations to 14 literature, company documents or depositions, 15 right? 16 A. Yes. Right. 17 Q. As it relates to the -- I'm trying to 18 distinguish for my question the scientific 19 literature from the company documents and 20 depositions. 21 Okay? 22 With respect to scientific 23 literature, what was your criteria for inclusion 24 or exclusion of literature in your report? 25 A. Well, the report starts with a</p>	<p style="text-align: right;">Page 108</p> <p>1 looking at the known, very well established 2 pathways by which the dimethylnitrosamines 3 metabolized can damage DNA, showing that that also 4 occurs in humans, that human metabolism with 5 dimethylnitrosamines are very well characterized. 6 Then looking at aspects of the 7 exposure, putting the dose response studies that 8 were carried out in rats, then looking at the more 9 specific aspects of the valsartan contamination 10 and the resulting exposure to dimethylnitrosamine 11 and blending these together to make a logic and 12 readable product. 13 Q. Were there things that you came 14 across -- 15 A. In order to do that, I don't need to 16 review every publication that's ever been written 17 on nitrosamines. 18 Q. Were there studies that you came 19 across in your research and work that found the 20 carcinogenicity of NDMA or NDEA in humans to be 21 inconclusive or unknown that you omitted from your 22 report? 23 MR. SLATER: Objection. 24 You can answer. 25 A. There are many studies that conclude</p>
<p style="text-align: right;">Page 107</p> <p>1 general consideration of nitrosamine 2 carcinogenesis. For that, I used literature that 3 I refer to frequently, certain reviews and certain 4 specific publications. 5 For the literature that refers more 6 specifically to valsartan, I referred to the -- a 7 couple of publications on valsartan as well as the 8 EMA report and maybe a couple of others. I don't 9 really remember. 10 Q. I think it's probably fair to say 11 that your report and the references that you cite 12 at the conclusion of the report was not intended 13 to include citation to every publication on the 14 subject of NDMA and NDEA ever written. 15 Fair to say? 16 A. Yes. 17 Q. So what I'm just wondering is was 18 there some method in your mind that you started 19 with as to what references you were going to rely 20 upon and cite and which ones you were going to 21 exclude? Did you have any methodology in that 22 regard? 23 A. Yes. I focused on the studies that 24 are relevant to cancer induction by 25 dimethylnitrosamine in humans. Basically, I'm</p>	<p style="text-align: right;">Page 109</p> <p>1 with, you know, statements like, you know, we 2 don't necessarily know whether this particular 3 exposure to products or environments containing 4 NDMA or other carcinogens for that matter actually 5 cause cancer. So I mean, they're all -- you know, 6 all studies have limitations and those limitations 7 are usually described. So I mean, I would say 8 that, you know, virtually every study that I 9 quoted would have some kind of limitation. That's 10 part of science. 11 Q. Right. It sounds like you would 12 agree with me then that there are studies that are 13 not included in your report that found NDMA or 14 NDEA carcinogenicity in humans to be unknown or 15 inconclusive that you didn't discuss or didn't 16 cite. 17 A. Sure, that's possible. 18 Q. The studies -- many of the studies 19 that you ultimately cite are animal studies, 20 correct? 21 MR. SLATER: Objection. 22 You can answer. 23 A. Yes. 24 Q. I think beginning on page seven of 25 your report you have a section titled</p>

<p style="text-align: right;">Page 110</p> <p>1 "Carcinogenicity of Nitrosamines and NDMA and 2 Cancer." 3 Is that right? 4 A. Yes. 5 Q. In this section of the report, you 6 seem to cite and rely upon a series of animal 7 studies to demonstrate the carcinogenicity of 8 NDMA? 9 A. Yes. 10 Q. Is it true that the -- I think we 11 talked about this a little bit in connection with 12 your comparative paper that we mentioned earlier, 13 but is it true that toxicity tests are often 14 performed on animals to gain an understanding of 15 cellular and tissue response to toxins? 16 A. Yes. 17 Q. In an animal study, do you agree that 18 there are many factors that affect the outcome of 19 the test or create uncertainty about its 20 extrapolation into a heterogenous human 21 population? 22 MR. SLATER: Objection. 23 You can answer. 24 A. Sure, there are uncertainties. For 25 sure.</p>	<p style="text-align: right;">Page 112</p> <p>1 Q. Metabolic rates also differ between 2 humans and animals, right? 3 A. It can. 4 Q. The binding efficiency of a foreign 5 substance like NDMA to DNA can also differ across 6 species? 7 MR. SLATER: Objection. 8 You can answer. 9 A. It can. 10 Q. For these and other reasons, most 11 competent scientists recognize that attempts to 12 extrapolate data from animal studies to humans is 13 fraught with peril? 14 MR. SLATER: Objection. 15 A. Fraught with peril? 16 Q. Yes, sir. 17 MR. SLATER: Someone wrote a good 18 question there. 19 A. Strong words. Strong words. 20 MR. SLATER: Objection to the 21 question. 22 You can answer. 23 Q. The question is -- 24 A. There are uncertainties. Sure, there 25 are uncertainties. I wouldn't say it's fraught</p>
<p style="text-align: right;">Page 111</p> <p>1 Q. Genomic instability differs from 2 species to species; true? 3 MR. SLATER: Objection. 4 You can answer. 5 A. Yes. 6 Q. DNA repair capacity differs from 7 species to species; true? 8 MR. SLATER: Objection. 9 A. It's a very general statement. 10 Q. Is it true? 11 A. I don't know. Probably. 12 Q. Metabolic factors differ from species 13 to species; true? 14 MR. SLATER: Objection. 15 You can answer. 16 A. Sure. There can be differences. 17 Q. For instance, the level of metabolic 18 enzymes are not identical from one species to 19 another, correct? 20 MR. SLATER: Objection. 21 You can answer. 22 A. In general, that's probably true. 23 Q. In fact, the level of enzymes are not 24 even homogeneous across the human population? 25 A. Yes, that's true.</p>	<p style="text-align: right;">Page 113</p> <p>1 with peril. 2 Q. Would you say it's fraught with 3 difficulty? 4 MR. SLATER: Objection. 5 You can answer. 6 A. No, I wouldn't say it's fraught with 7 difficulty. 8 Q. Well, let me show you -- 9 A. I would say that -- you like the word 10 "fraught." There are uncertainties I would say. 11 Q. Sure. 12 A. Those are well recognized. 13 (Whereupon, Exhibit 6 was marked for 14 identification.) 15 Q. Let me show you what I'll mark as -- 16 I think we're up to Exhibit 6. It's a paper by 17 Gobar -- G-O-M-B-A-R -- is the lead author. The 18 paper is entitled "Pharmacokinetics of 19 Nitrosodimethylamine in Beagles." 20 Are you familiar with that paper? 21 A. Yes. 22 Q. I think you cited it in your report, 23 correct? 24 A. Correct. 25 Q. You relied upon it, correct?</p>

<p style="text-align: right;">Page 114</p> <p>1 A. Relied upon it? Sure, I cited it. 2 Yes. 3 MR. TRISCHLER: Can you put up the 4 Exhibit 6 please, the first page of it? 5 THE VIDEOGRAPHER: Looking for it 6 now. One moment. 7 You said in beagles? 8 MR. TRISCHLER: Yes. 9 THE VIDEOGRAPHER: I'm actually not 10 seeing this in the list I was given, one 11 related to beagles. 12 THE WITNESS: Go to PubMed and enter 13 Gombar -- 14 MR. TRISCHLER: I'll send it now. 15 THE VIDEOGRAPHER: Thank you. 16 MR. TRISCHLER: You should have it. 17 THE VIDEOGRAPHER: One moment while 18 it's downloading. That was not one that was 19 uploaded before. Maybe it failed in the 20 upload. 21 MR. TRISCHLER: Must have been the 22 one that broke the computer. 23 THE VIDEOGRAPHER: Maybe. 24 MR. TRISCHLER: Okay. 25 BY MR. TRISCHLER:</p>	<p style="text-align: right;">Page 116</p> <p>1 deals with the topic. 2 Q. And you agree with me that the 3 attempt to -- that there are problems and 4 limitations associated with the extrapolation of 5 carcinogenicity data from animals to humans; true? 6 MR. SLATER: Objection. 7 A. There are limitations. Sure, there 8 are limitations. 9 Q. Gombar and his colleagues go on to 10 tell us what some of those limitations are, 11 correct? 12 A. Yes. 13 Q. Some of those limitations include the 14 inherited susceptibility of tissues to the 15 carcinogenic action of NDMA, the efficiency and 16 fidelity of repair processes, quantitative and 17 qualitative metabolic aspects and the 18 pharmacokinetics of the compound may be very 19 different in humans, right? 20 A. Yes. It's all true. That's why we 21 do research. 22 Q. Sure. 23 Do you consider yourself a scientist, 24 Dr. Hecht? 25 A. Yes.</p>
<p style="text-align: right;">Page 115</p> <p>1 Q. So now, Dr. Hecht, we're looking at 2 the first page of Gombar's study that you cite in 3 your report. There's a section on the left-hand 4 side of the first page marked "Introduction," if 5 you could highlight that section for the doctor. 6 Certainly, Doctor, when I show you a 7 document like this, you're free to read as much of 8 the study as you want, but I wanted to direct your 9 attention to the introduction in the second 10 paragraph where Gombar and his colleagues note 11 that extrapolation of carcinogenicity data from 12 animals to humans is fraught with difficulty. 13 Do you see that? 14 A. Yes, those are the words he used. 15 Q. Right. 16 Do you agree with Gombar's 17 statements? 18 A. Not necessarily. I think "fraught 19 with difficulty" is a little too strong. You 20 know, that's his opinion, so it's okay. 21 Q. But you're the one that cited to this 22 report, not me, correct? 23 MR. SLATER: Objection. 24 Argumentative. 25 A. I cited it, yeah, that's true. It</p>	<p style="text-align: right;">Page 117</p> <p>1 Q. As a scientist, do you agree that 2 it's improper to draw conclusions and inferences 3 from a study that the authors themselves did not 4 support? 5 MR. SLATER: Objection. 6 A. I'm not -- could you repeat that? 7 Q. Sure. 8 Do you agree that it would be 9 improper to draw conclusions or inferences from a 10 study that the authors themselves did not support? 11 MR. SLATER: Hold on, Dr. Hecht. 12 Objection and counsel might want to 13 read Law 360 and the Eighth Circuit's 14 decision from yesterday. 15 You can answer, Dr. Hecht. 16 A. So we draw conclusions from our data. 17 All the data has limitations and we think about 18 and analyze the limitations of the data and that 19 influences our conclusions. 20 Q. Do you ever draw conclusions from a 21 study that the authors of that study themselves 22 reject? 23 MR. SLATER: Objection. 24 You can answer. 25 A. Not in general. Not in general, no.</p>

<p style="text-align: right;">Page 118</p> <p>1 Q. In general, you'd agree that would --</p> <p>2 A. Well, no, actually -- so, you know,</p> <p>3 that depends on the data that's being presented.</p> <p>4 I mean, I might find errors in their data and then</p> <p>5 I wouldn't come to the same conclusions.</p> <p>6 Q. In general, would you --</p> <p>7 A. I might find flaws in their</p> <p>8 experimental approach and then I would reject</p> <p>9 their conclusions. Just because it's published</p> <p>10 doesn't mean that it's necessarily correct.</p> <p>11 Q. One of the papers that you also cited</p> <p>12 was a paper by Magee and Barnes entitled -- you</p> <p>13 can take that one down -- entitled "The Production</p> <p>14 of Malignant Primary Hepatic Tumors in the Rat by</p> <p>15 Feeding Dimethylnitrosamine."</p> <p>16 Do you recall that paper?</p> <p>17 A. Yes, very well.</p> <p>18 MR. TRISCHLER: I'll mark that as our</p> <p>19 next numbered exhibit. I think we're up to</p> <p>20 7.</p> <p>21 (Whereupon, Exhibit 7 was marked for</p> <p>22 identification.)</p> <p>23 Q. In this paper, I believe that the</p> <p>24 rats were administered NDMA on the order of</p> <p>25 25 milligrams per kilogram of body weight.</p>	<p style="text-align: right;">Page 120</p> <p>1 Barnes study and what any plaintiff in this case</p> <p>2 may have received?</p> <p>3 MR. SLATER: Objection.</p> <p>4 You can answer.</p> <p>5 A. I don't know what you mean by "no</p> <p>6 correlation." This was, as you know, as you're</p> <p>7 well aware, the first study showing that</p> <p>8 dimethylnitrosamine causes liver tumors in rats.</p> <p>9 So naturally, they started with a high dose.</p> <p>10 That's -- if you don't start with a high dose,</p> <p>11 then you get a negative result and you still</p> <p>12 haven't answered the question.</p> <p>13 If you start with a high dose and you</p> <p>14 get a negative result, you can be pretty sure that</p> <p>15 the compound is not a strong carcinogen. Years</p> <p>16 later, as you know, after literally many, many</p> <p>17 studies have extended and confirmed this initial</p> <p>18 study showing that dimethylnitrosamine causes</p> <p>19 liver cancer in rats, there was the study -- the</p> <p>20 dose response study by Peto, Grasso and others --</p> <p>21 showing going down to extremely low doses.</p> <p>22 So I don't really see what you're</p> <p>23 driving at here, sir.</p> <p>24 MR. TRISCHLER: Object and move to</p> <p>25 strike as non-responsive.</p>
<p style="text-align: right;">Page 119</p> <p>1 Is that right?</p> <p>2 A. Yes.</p> <p>3 Q. Do you know how many nanograms are in</p> <p>4 a milligram?</p> <p>5 A. Sure. There's a thousand nanograms</p> <p>6 in a microgram and there's 1,000 micrograms in a</p> <p>7 milligram, so there are a million nanograms in</p> <p>8 a milligram.</p> <p>9 Q. So the dose that was administered to</p> <p>10 the rats in the Magee and Barnes study was --</p> <p>11 A. Yes, that's correct.</p> <p>12 Q. Do you know the equivalent dose of</p> <p>13 25 million nanograms per kilogram in a human being</p> <p>14 that weighs 150 pounds?</p> <p>15 A. Not offhand, no. I would have to do</p> <p>16 the calculation. I can't do it sitting here,</p> <p>17 talking to you.</p> <p>18 Q. Would you agree that that dose is on</p> <p>19 order of magnitude far greater than any dose that</p> <p>20 would have been given to any plaintiff who took</p> <p>21 valsartan-containing medications containing some</p> <p>22 nitrosamines?</p> <p>23 A. Absolutely.</p> <p>24 Q. Do you agree that there's no</p> <p>25 correlation between the dose administered in the</p>	<p style="text-align: right;">Page 121</p> <p>1 Q. All I was asking you about was the</p> <p>2 Magee and Barnes study, Doctor.</p> <p>3 My question was the doses that Magee</p> <p>4 and Barnes administered to the rats in this study</p> <p>5 were far and away greater than the levels of</p> <p>6 nitrosamines that were observed in any</p> <p>7 valsartan-containing medications.</p> <p>8 Would you agree?</p> <p>9 A. Absolutely.</p> <p>10 Q. And in this same study that we marked</p> <p>11 as Exhibit 7, did -- I think the authors also</p> <p>12 tried to duplicate their work on other mammals,</p> <p>13 namely rabbits, right?</p> <p>14 MR. SLATER: Objection.</p> <p>15 You can answer.</p> <p>16 A. Yes.</p> <p>17 Q. And there was NDMA that was</p> <p>18 administered to rabbits in this Magee and Barnes</p> <p>19 study, correct?</p> <p>20 A. Yes.</p> <p>21 Q. How much NDMA was delivered to these</p> <p>22 rabbits?</p> <p>23 A. I don't remember.</p> <p>24 Q. Was it --</p> <p>25 A. It was a high dose. I think they</p>

<p style="text-align: right;">Page 122</p> <p>1 also had some toxicity.</p> <p>2 Q. Was it the same 25 milligrams per</p> <p>3 kilogram of body weight dose that the --</p> <p>4 A. I don't know. Look in the paper. I</p> <p>5 don't remember.</p> <p>6 Q. Do you remember that in connection</p> <p>7 with the rabbits no tumors were observed in this</p> <p>8 study?</p> <p>9 MR. SLATER: Objection.</p> <p>10 You can answer.</p> <p>11 A. I forgot about the rabbits.</p> <p>12 MR. TRISCHLER: If you could</p> <p>13 highlight the second paragraph for me,</p> <p>14 please.</p> <p>15 Q. Take a look at it, Doctor.</p> <p>16 Were any tumors observed in the</p> <p>17 rabbits in this study?</p> <p>18 A. No.</p> <p>19 MR. TRISCHLER: You mentioned the</p> <p>20 Peto paper, so let me ask you about that.</p> <p>21 There's a paper by a gentleman named</p> <p>22 Peto that you just mentioned, P-E-T-O. We</p> <p>23 can mark that as Exhibit 8.</p> <p>24 (Whereupon, Exhibit 8 was marked for</p> <p>25 identification.)</p>	<p style="text-align: right;">Page 124</p> <p>1 that was administered to rats, but it did not</p> <p>2 provide any reliable information on the effects of</p> <p>3 nitrosamines on humans, correct?</p> <p>4 MR. SLATER: Objection.</p> <p>5 You can answer.</p> <p>6 A. Correct.</p> <p>7 Q. I didn't hear your answer, sir.</p> <p>8 A. Yes, correct.</p> <p>9 Actually, I wouldn't say any reliable</p> <p>10 information. I hate to get into a semantic</p> <p>11 argument. I wouldn't say it doesn't provide any</p> <p>12 reliable information. It does provide reliable</p> <p>13 information, well, definitely with respect to</p> <p>14 rats. You know, whether this information is</p> <p>15 directly applicable to humans, we don't know, but</p> <p>16 it does give a strong indication of the strength</p> <p>17 of the carcinogen and a widely accepted animal</p> <p>18 model.</p> <p>19 Q. What Peto said and what he wrote in</p> <p>20 the peer-reviewed literature was that this data</p> <p>21 does not provide reliable information as to the</p> <p>22 effects of a part per billion nitrosamine</p> <p>23 concentration on humans.</p> <p>24 Isn't that --</p> <p>25 A. That's what he says.</p>
<p style="text-align: right;">Page 123</p> <p>1 Q. While the gentleman is taking care of</p> <p>2 that for us, Doctor, you not only mentioned the</p> <p>3 Peto paper a little earlier, you cited to it in</p> <p>4 your report, correct?</p> <p>5 A. Yes.</p> <p>6 Q. In Peto, we have another animal study</p> <p>7 where NDMA and NDEA were administered to rats,</p> <p>8 correct?</p> <p>9 A. Yes.</p> <p>10 Q. In his work, Peto was careful to note</p> <p>11 that no extrapolation of this data to humans</p> <p>12 should be done.</p> <p>13 Do you agree?</p> <p>14 A. Yes.</p> <p>15 Q. In fact, if you can go to page 6445</p> <p>16 of that paper, the second paragraph of the</p> <p>17 chart -- there we go -- what Peto wrote is that</p> <p>18 "It would be a serious distortion of these</p> <p>19 experimental results to extrapolate this data to</p> <p>20 humans."</p> <p>21 Correct?</p> <p>22 A. That's what he wrote.</p> <p>23 Q. And so what we know from the Peto</p> <p>24 study is it provided us with some valuable</p> <p>25 information on dose response relationship to NDMA</p>	<p style="text-align: right;">Page 125</p> <p>1 Q. And he says it would be a distortion</p> <p>2 of these experimental results to suggest something</p> <p>3 different?</p> <p>4 A. Yes, that's what he said.</p> <p>5 Q. My question was not asking you about</p> <p>6 whether Peto's study provides us dose effect --</p> <p>7 provides us with relevant and reliable dose effect</p> <p>8 data on NDMA in rats.</p> <p>9 I'm talking about humans. When we</p> <p>10 talk about humans, Peto's study does not provide</p> <p>11 us with any reliable information. He even said</p> <p>12 so, right?</p> <p>13 MR. SLATER: Objection.</p> <p>14 A. That's what he says. It says it</p> <p>15 right there.</p> <p>16 MR. TRISCHLER: I'm going to ask you</p> <p>17 about another animal study that you cited in</p> <p>18 your report. I think we'll mark this</p> <p>19 one Exhibit 9 and it's another paper by</p> <p>20 Gombar, G-O-M-B-A-R, entitled</p> <p>21 "Pharmacokinetics of N-nitrosodimethylamine</p> <p>22 in Swine."</p> <p>23 (Whereupon, Exhibit 9 was marked for</p> <p>24 identification.)</p> <p>25 Q. Do you see that?</p>

<p style="text-align: right;">Page 126</p> <p>1 A. Yes.</p> <p>2 Q. In this paper, is it also true, if</p> <p>3 you recall, that the authors once again cautioned</p> <p>4 against extrapolating carcinogenicity data from</p> <p>5 animals to humans?</p> <p>6 MR. SLATER: Objection.</p> <p>7 You can answer.</p> <p>8 A. I don't recall, but I presume that</p> <p>9 they did.</p> <p>10 Q. If you go to page 1353, under the</p> <p>11 "Discussion" section of the paper, first paragraph</p> <p>12 there, Gombar says once again that extrapolation</p> <p>13 of carcinogenicity data from laboratory animals to</p> <p>14 humans is a difficult task because chemical</p> <p>15 carcinogenesis is a multistep process involving</p> <p>16 many factors, right?</p> <p>17 A. True.</p> <p>18 Q. Do you agree with all that?</p> <p>19 A. Pardon?</p> <p>20 Q. Do you agree with all that, sir?</p> <p>21 A. Yes, I do.</p> <p>22 Q. While there are many factors that</p> <p>23 make extrapolation of data from animal studies to</p> <p>24 humans difficult, one of the things that Gombar</p> <p>25 and his colleagues note here particularly is the</p>	<p style="text-align: right;">Page 128</p> <p>1 Yes. I mean, that was written about</p> <p>2 20 years ago, I think.</p> <p>3 Q. It was written in 1988, I think.</p> <p>4 A. Okay. So, you know, 33 years ago.</p> <p>5 Q. Was it correct when written in 1988</p> <p>6 that --</p> <p>7 A. Yeah.</p> <p>8 MR. SLATER: Let him finish the</p> <p>9 question so I can place an objection.</p> <p>10 MR. TRISCHLER: Sorry. We have to go</p> <p>11 back to pausing there, Doctor. Sometimes --</p> <p>12 and I know it can be difficult with the, you</p> <p>13 know, trying to do this remotely, but let me</p> <p>14 finish my question.</p> <p>15 Q. My question was was it true, was</p> <p>16 Gombar's statement when he wrote it in 1988 that</p> <p>17 it's not yet been proven that nitrosamines cause</p> <p>18 any human cancer, was that a true and correct</p> <p>19 statement when written in 1988?</p> <p>20 MR. SLATER: Objection.</p> <p>21 A. Yes.</p> <p>22 Q. And in the second -- this is the</p> <p>23 second paper that we looked at from Gombar that</p> <p>24 you cited in your report and much like the first</p> <p>25 one, can we agree that the doses that were</p>
<p style="text-align: right;">Page 127</p> <p>1 differing pharmacokinetics from species to</p> <p>2 species, correct?</p> <p>3 A. Right.</p> <p>4 Q. Can we agree that the authors of the</p> <p>5 animal studies that you cite in your report have</p> <p>6 repeatedly and consistently cautioned against</p> <p>7 using this animal data to extrapolate to</p> <p>8 carcinogenicity in humans?</p> <p>9 A. They do, yeah.</p> <p>10 Q. And there's one other statement in</p> <p>11 this Exhibit 9 that I wanted to ask you about.</p> <p>12 It's -- I think it's on the first page of the</p> <p>13 paper under the introduction section if you -- and</p> <p>14 in this study that you cite in your own report,</p> <p>15 what Gombar said and what he observes is that it's</p> <p>16 not yet proven that nitrosamines cause any human</p> <p>17 cancer.</p> <p>18 Do you see that?</p> <p>19 A. Yes.</p> <p>20 Q. Do you agree with that statement?</p> <p>21 MR. SLATER: Objection.</p> <p>22 A. Yes.</p> <p>23 Sorry, I just had a cramp.</p> <p>24 Q. Are you okay?</p> <p>25 A. Yes, I'm okay.</p>	<p style="text-align: right;">Page 129</p> <p>1 administered to these animals were far greater</p> <p>2 than any human equivalent dose?</p> <p>3 A. They were greater, yes.</p> <p>4 Q. Far greater?</p> <p>5 A. But not as greater as the Magee and</p> <p>6 Barnes paper. The Magee and Barnes paper, they</p> <p>7 were looking at possible carcinogenicity of a</p> <p>8 compound. They didn't know whether it was</p> <p>9 carcinogenic or not, so they started with a high</p> <p>10 dose.</p> <p>11 In these papers by Gombar, I don't</p> <p>12 really remember the dose, but I'm pretty sure it</p> <p>13 was less than what Magee and Barnes used because</p> <p>14 this was a pharmacokinetic study. They would have</p> <p>15 used multiple doses, probably ones that were less</p> <p>16 than used by Magee and Barnes.</p> <p>17 Q. Well, if you look at the summary of</p> <p>18 the paper there in the top left-hand column, the</p> <p>19 doses are covered.</p> <p>20 The doses were -- there were doses of</p> <p>21 NDMA administered both intravenously and orally,</p> <p>22 correct?</p> <p>23 A. Yes.</p> <p>24 Q. And the doses were on the magnitude</p> <p>25 intravenously that totaled 1.6 milligrams per</p>

<p style="text-align: right;">Page 130</p> <p>1 kilogram, right?</p> <p>2 A. 0.1, 0.5 and 1.0. Those were</p> <p>3 separate. I don't know why you're adding them</p> <p>4 together.</p> <p>5 Q. I was adding them together as a total</p> <p>6 IV dose.</p> <p>7 A. Well, that's wrong. I mean, I think</p> <p>8 they had different animals, different specific</p> <p>9 animals that were each treated with these three</p> <p>10 different doses. In other words, the lowest dose</p> <p>11 would have been 0.1 milligrams per kilogram, not</p> <p>12 1.6.</p> <p>13 Q. All right.</p> <p>14 Then the oral doses were 1.0</p> <p>15 milligram per kilogram and 5 milligrams per</p> <p>16 kilogram?</p> <p>17 A. Yes.</p> <p>18 Q. There are a million nanograms in a --</p> <p>19 A. Yes, they're higher than the human</p> <p>20 dose. We don't have to go through it again.</p> <p>21 Q. Please let me finish my question.</p> <p>22 A. Okay.</p> <p>23 Q. There are orders of the doses are</p> <p>24 orders of magnitude higher than what any human</p> <p>25 would see from valsartan-containing medications,</p>	<p style="text-align: right;">Page 132</p> <p>1 Q. To this day, do you agree that</p> <p>2 there's no scientific evidence conclusively</p> <p>3 establishing NDMA as a cause of human cancer?</p> <p>4 MR. SLATER: Objection.</p> <p>5 You can answer.</p> <p>6 A. Well, let me answer it this way.</p> <p>7 I'll read from the IARC report in 1978.</p> <p>8 "Although no epidemiologic data was</p> <p>9 available N-nitrosodimethylamine should be</p> <p>10 regarded for practical purposes as if it were</p> <p>11 carcinogenic to humans," IARC, 1978, World Health</p> <p>12 Organization.</p> <p>13 Q. Do you agree that there's no</p> <p>14 scientific evidence conclusively establishing NDEA</p> <p>15 as a known cause of human cancer?</p> <p>16 MR. SLATER: Objection.</p> <p>17 You can answer.</p> <p>18 A. Yes.</p> <p>19 Q. Can you cite me to any peer-reviewed</p> <p>20 publication available in the scientific literature</p> <p>21 identifying NDMA as a known cause of human</p> <p>22 cancers?</p> <p>23 MR. SLATER: Objection.</p> <p>24 You can answer.</p> <p>25 A. No.</p>
<p style="text-align: right;">Page 131</p> <p>1 right?</p> <p>2 MR. SLATER: Objection.</p> <p>3 A. Correct. Yes, that's correct.</p> <p>4 MR. TRISCHLER: You can take that</p> <p>5 document down, I believe, sir.</p> <p>6 Thank you.</p> <p>7 Q. So what we just learned from the</p> <p>8 Gombar paper was that -- and what we agreed on was</p> <p>9 that in 1988 there was no evidence demonstrating</p> <p>10 that nitrosamines caused any human cancer, right?</p> <p>11 A. I wouldn't say no evidence. I</p> <p>12 wouldn't say that.</p> <p>13 Q. All right. Let me rephrase the</p> <p>14 question.</p> <p>15 A. We had evidence from -- at that time,</p> <p>16 we had evidence from tobacco-specific nitrosamines</p> <p>17 of cancer in humans.</p> <p>18 Q. Let me ask my question specific to</p> <p>19 NDMA then.</p> <p>20 In 1988, we can agree that it had not</p> <p>21 been proven that NDMA caused any human cancer,</p> <p>22 right?</p> <p>23 MR. SLATER: Objection.</p> <p>24 You can answer.</p> <p>25 A. Yes, correct.</p>	<p style="text-align: right;">Page 133</p> <p>1 Q. Can you cite me to any peer-reviewed</p> <p>2 publication available in the scientific literature</p> <p>3 identifying NDEA as a known cause of human</p> <p>4 cancers?</p> <p>5 A. No.</p> <p>6 Q. Are you aware of any epidemiological</p> <p>7 study that's found NDMA to be a known cause of</p> <p>8 cancer in humans?</p> <p>9 A. Not by itself, but there are a number</p> <p>10 of epidemiology studies that looked at dietary</p> <p>11 exposure to NDMA and cancer.</p> <p>12 Q. Have those -- are you aware of any of</p> <p>13 those studies that have concluded that NDMA is a</p> <p>14 known cause of cancer in humans?</p> <p>15 MR. SLATER: Objection.</p> <p>16 You can answer.</p> <p>17 A. Not specifically as you stated it,</p> <p>18 no.</p> <p>19 Q. Right.</p> <p>20 There are studies that suggest there</p> <p>21 might be an association between NDMA intake and</p> <p>22 some cancers.</p> <p>23 My question was are you aware of any</p> <p>24 epidemiological study that has found NDMA to be a</p> <p>25 known cause of cancer in humans?</p>

<p style="text-align: right;">Page 134</p> <p>1 MR. SLATER: Objection. 2 You can answer. 3 A. No. 4 Q. Are you aware of any epidemiological 5 study that has found NDEA to be a known cause of 6 cancer in humans? 7 A. No. 8 Q. Have you ever seen an article or a 9 case study published anywhere in the literature 10 that concludes that a patient's cancer was caused 11 by NDMA? 12 MR. SLATER: Objection. 13 You can answer. 14 A. No. 15 Q. Have you seen any article or case 16 study published anywhere in the literature that 17 has concluded that a patient's cancer was caused 18 by NDEA? 19 MR. SLATER: Objection. 20 You can answer. 21 A. No. 22 Q. You mentioned the IARC report a 23 little bit earlier. 24 Do you remember that? 25 A. Yes.</p>	<p style="text-align: right;">Page 136</p> <p>1 epidemiological studies to assess carcinogenicity 2 in humans; true? 3 A. Yes. 4 Q. IARC has also published a monograph 5 for NDEA, right? 6 A. Yes. Yes. 7 Q. Were you part of the working group 8 for the NDEA monograph? 9 A. No. 10 Q. In the NDEA monograph, the working 11 group of scientists who studied this agent 12 observed that there was no case reports available 13 to assess carcinogenicity in humans, correct? 14 A. Correct. 15 Q. The working group also went on to 16 note there were no available epidemiological 17 studies to assess carcinogenicity of NDEA in 18 humans; true? 19 A. Yes. 20 Q. So based on these monographs, IARC 21 classified both NDMA and NDEA as Class 2A probable 22 carcinogens. 23 A. Probable human carcinogens. Probable 24 human carcinogens. 25 Q. Class 2A?</p>
<p style="text-align: right;">Page 135</p> <p>1 Q. IARC is the International Agency for 2 Research on Cancer, correct? 3 A. Yes. 4 Q. You mentioned the World Health 5 Organization. I think IARC is an arm of the World 6 Health Organization, right? 7 A. Yes. 8 Q. IARC has working groups that review 9 available scientific data, prepare monographs and 10 those monographs are then used to classify 11 compounds as carcinogenic or noncarcinogenic, 12 correct? 13 A. Right. 14 Q. IARC has published a monograph 15 for NDMA you pointed out for us on the video a 16 little bit ago, right? 17 A. That was an early one. It also did 18 an update some years later. 19 Q. Okay. Sorry. I didn't realize you 20 were not finished. 21 Were you part of the working group 22 for the NDMA monograph? 23 A. No. 24 Q. In the monograph, the IARC working 25 group noted that there was no case reports or</p>	<p style="text-align: right;">Page 137</p> <p>1 A. Yes. Probable human carcinogens, not 2 probable carcinogens. 3 Q. But they were assigned to Class 2A -- 4 A. Probably carcinogenic to humans. 5 That's what they said. 6 Q. Did you hear my last question? 7 A. 2A. Yeah, 2A. 8 Q. When did IARC develop this 9 classification system? 10 A. I believe it was around 1970. 11 Q. There's a big, long list of compounds 12 that were -- that IARC has classified since 1970, 13 correct? 14 A. Yes. 15 MR. TRISCHLER: I don't know if we 16 have that list or not. 17 On the next break, I'll have that 18 list marked as an exhibit because I don't 19 know if I sent it to the video folks -- 20 THE VIDEOGRAPHER: Counsel, on that 21 note, I have about five minutes left on this 22 media, just to let you know. 23 Q. In any event, when was the Class 2A 24 designation assigned -- first assigned to NDMA? 25 A. That would be 1978.</p>

<p style="text-align: right;">Page 138</p> <p>1 Q. You said it was updated after 1978?</p> <p>2 A. Yes.</p> <p>3 Q. I think that was in 1987?</p> <p>4 A. Sounds about right.</p> <p>5 Q. Was the classification changed in --</p> <p>6 A. No. Still 2A.</p> <p>7 Q. When was NDEA first classified as 2A?</p> <p>8 A. Same.</p> <p>9 Q. 1970?</p> <p>10 A. 1978.</p> <p>11 Q. Seventy-eight. Okay.</p> <p>12 Was it updated in 1987?</p> <p>13 A. I believe so.</p> <p>14 Q. When it was updated in 1987 was the</p> <p>15 classification of NDEA as a 2A class carcinogen,</p> <p>16 was it changed?</p> <p>17 A. No. They're both 2A.</p> <p>18 Q. To this day, has the classification</p> <p>19 of NDEA or NDMA ever changed?</p> <p>20 A. No. Both 2A.</p> <p>21 Q. From your perspective, the Class 1</p> <p>22 designation is reserved for known human</p> <p>23 carcinogens, correct?</p> <p>24 A. Yes.</p> <p>25 Q. The known carcinogens that are</p>	<p style="text-align: right;">Page 140</p> <p>1 lunch schedule?</p> <p>2 MR. SLATER: I want to do whatever</p> <p>3 Dr. Hecht wants to do.</p> <p>4 MR. TRISCHLER: Okay.</p> <p>5 Do you want to -- I'm just asking did</p> <p>6 you want to --</p> <p>7 MR. SLATER: We'll talk during the</p> <p>8 break how much longer he wants to go before</p> <p>9 we eat.</p> <p>10 Is that all right?</p> <p>11 MR. TRISCHLER: It's okay with me.</p> <p>12 THE WITNESS: I'm good until about</p> <p>13 one o'clock your time.</p> <p>14 MR. TRISCHLER: Okay.</p> <p>15 Why don't we take a five-minute break</p> <p>16 to do whatever the technical people need to</p> <p>17 do and we can go until one o'clock my time,</p> <p>18 if that's okay with the witness and if it's</p> <p>19 okay with Adam.</p> <p>20 MR. SLATER: It's fine.</p> <p>21 THE WITNESS: How long are we going</p> <p>22 to break for lunch?</p> <p>23 MR. TRISCHLER: As long as you want.</p> <p>24 THE WITNESS: Okay.</p> <p>25 MR. TRISCHLER: Or as short as you</p>
<p style="text-align: right;">Page 139</p> <p>1 included in Class 1 include tobacco, correct?</p> <p>2 A. Yes.</p> <p>3 Q. Is alcohol a Class 1 carcinogen?</p> <p>4 A. Yes.</p> <p>5 Q. Asbestos, is that a Class 1</p> <p>6 carcinogen?</p> <p>7 A. Yes.</p> <p>8 Q. Coal?</p> <p>9 A. Coal tar.</p> <p>10 Q. Is listed as a Class 1 carcinogen?</p> <p>11 A. Coal tar. Not coal itself.</p> <p>12 Q. Okay.</p> <p>13 The fact is IARC has identified over</p> <p>14 100 known carcinogens, right?</p> <p>15 A. You mean Class 1?</p> <p>16 Q. Yes, sir.</p> <p>17 A. I believe that's right.</p> <p>18 Q. To this day, neither NDMA nor NDEA</p> <p>19 have ever been listed by IARC as known human</p> <p>20 carcinogen, right?</p> <p>21 A. Not Class 1, no.</p> <p>22 MR. TRISCHLER: We need to take a</p> <p>23 break to change tapes or do whatever the</p> <p>24 video person needs to do.</p> <p>25 Adam, what did you want to do about a</p>	<p style="text-align: right;">Page 141</p> <p>1 want.</p> <p>2 THE WITNESS: Okay. I need to go out</p> <p>3 and get something.</p> <p>4 MR. TRISCHLER: Okay. Sure, we</p> <p>5 can -- you're in charge of that aspect, so --</p> <p>6 THE WITNESS: Okay.</p> <p>7 THE VIDEOGRAPHER: The time is 12:17.</p> <p>8 This ends media two.</p> <p>9 (Recess taken)</p> <p>10 THE VIDEOGRAPHER: The time is now</p> <p>11 12:27.</p> <p>12 This begins media three.</p> <p>13 You may proceed.</p> <p>14 Q. Doctor, before our last break, we</p> <p>15 were talking a little bit about the IARC</p> <p>16 classification of agents.</p> <p>17 Do you recall that?</p> <p>18 A. Yes.</p> <p>19 Q. I asked you if there was a published</p> <p>20 list where IARC identifies all of the agents that</p> <p>21 have been studied by their grouping or</p> <p>22 classification.</p> <p>23 Do you recall that?</p> <p>24 A. Yes.</p> <p>25 MR. TRISCHLER: So I've gone ahead</p>

<p style="text-align: right;">Page 142</p> <p>1 and sent to our technical folks that list and 2 I'll have that marked as the next numbered 3 exhibit. I think it might be 10. 4 THE VIDEOGRAPHER: Ten is correct, 5 sir. 6 (Whereupon, Exhibit 10 was marked for 7 identification.) 8 Q. I think what you're now looking at is 9 the first page of that exhibit. It's 37 pages 10 long -- and I think if you could just blow up, 11 Bill, some part of it for the witness's benefit -- 12 this is the list that I was showing you or 13 mentioning before, Doctor, and it tells us that 14 IARC has prepared monographs for each of these 15 agents and classified them by their carcinogenic 16 properties, correct? 17 A. Yes. 18 Q. As we mentioned, included in this 19 37-page compendium is NDMA and NDEA, both of which 20 are Class 2A, right? 21 A. Yes. 22 Q. Is it true that the classification of 23 an agent as Class 2A is a classification that's 24 reserved for agents where there's limited evidence 25 of carcinogenicity in humans and sufficient</p>	<p style="text-align: right;">Page 144</p> <p>1 all. I don't agree. No, I don't agree. 2 Q. What -- 3 A. I don't agree that it's limited. 4 Q. Okay. 5 Is there a process within IARC to 6 petition a working group to change a 7 classification? 8 A. I have no idea. 9 Q. At any point in your career have you 10 ever submitted any petition, evidence or writings 11 to IARC advocating a change in a classification 12 for an agent? 13 A. No. 14 Q. To this point in time, have you 15 submitted any petition, evidence or writings to 16 IARC advocating a change in the classification for 17 NDMA or NDEA? 18 A. No, I haven't. 19 Q. Outside the context of this 20 litigation, have you ever submitted anything to 21 any world health authority advocating or 22 suggesting that the scientific evidence justified 23 reclassifying NDMA and NDEA to known human 24 carcinogenic status? 25 A. No, I haven't.</p>
<p style="text-align: right;">Page 143</p> <p>1 carcinogenicity in experimental animals? 2 A. I think that's how they describe it. 3 Q. Do you agree with IARC's 4 classification of NDMA and NDEA as Class 2A? 5 A. Yes, I agree. But I also agree with 6 the statement that they should be regarded for 7 practical purposes as if it were carcinogenic in 8 humans. That was for NDMA. 9 Q. Do you agree -- 10 A. But yes, I agree that 2A is proper 11 because 2A is probably carcinogenic to humans. 12 Group one is carcinogenic to humans, so you would 13 need an instance where there's been exposure to 14 NDMA or NDEA in the absence of other possibly 15 causes and, you know, this could be the example, 16 valsartan. 17 Q. Do you agree that there is limited 18 evidence of carcinogenicity in humans for NDMA and 19 NDEA? 20 MR. SLATER: Objection. 21 You can answer. 22 A. You know, I'm not sure about limited. 23 So, I mean, I know that they do go through each 24 sub category in their final evaluation. I don't 25 really think it's -- I don't think it's limited at</p>	<p style="text-align: right;">Page 145</p> <p>1 Q. When we talk about Class 1 known 2 human carcinogens, we mention that among the 3 37-page compendium there are hundreds that have 4 been named as Class 1, right? 5 A. How many? I don't know. 6 Q. Over 100, I said. 7 A. If that's what you say. 8 Q. Okay. 9 A. You've got the list there. 10 Q. Would you agree that many of the 11 Class 1 carcinogens are things that all of us are 12 consuming and are exposed to on a daily basis? 13 A. All of them or many of them? What's 14 your question? 15 Q. Would you agree that many of the 16 Class 1 carcinogens are things that all of us 17 consume or are exposed to on a daily basis? 18 A. No. 19 Q. Is sunlight a Class 1 carcinogen? 20 A. Yes. 21 Q. Most of us are exposed to sunlight 22 every day, right? 23 MR. SLATER: Objection. 24 A. Unless you have xeroderma pigmentosa, 25 yes.</p>

<p style="text-align: right;">Page 146</p> <p>1 Q. Most of us don't?</p> <p>2 A. Correct.</p> <p>3 Q. But most of us are exposed to</p> <p>4 sunlight, a known human carcinogen, on a daily</p> <p>5 basis, right?</p> <p>6 A. Yes.</p> <p>7 Q. Processed meat, I think, is a Class 1</p> <p>8 known carcinogen, right?</p> <p>9 A. I don't know whether it's 1 or 2A.</p> <p>10 Q. You're not sure about that one?</p> <p>11 A. No. You can look on your list.</p> <p>12 Q. Let me take a look.</p> <p>13 Can you go to page 30, sir?</p> <p>14 Highlight the top third of that page for the</p> <p>15 witness. I think we can --</p> <p>16 According to Exhibit 10 from the IARC</p> <p>17 monograph, processed meat is a group one --</p> <p>18 A. Group one.</p> <p>19 Q. -- carcinogen, right?</p> <p>20 A. Group one. Yes.</p> <p>21 Q. So the bacon that I enjoy for</p> <p>22 breakfast is a known carcinogen?</p> <p>23 A. That would be a processed meat, yes.</p> <p>24 Q. The deli meat that I have for lunch</p> <p>25 is a known carcinogen, according to IARC?</p>	<p style="text-align: right;">Page 148</p> <p>1 that's true. But everything depends on dose.</p> <p>2 Q. I couldn't agree with you more.</p> <p>3 There are a lot of other foods and beverages that</p> <p>4 we consume every day that are Class 1 and Class 2A</p> <p>5 carcinogens according to IARC, correct?</p> <p>6 A. Yes.</p> <p>7 Q. The hot coffee or hot tea that we</p> <p>8 enjoy in the morning is a carcinogen according to</p> <p>9 IARC, right?</p> <p>10 MR. SLATER: Objection.</p> <p>11 You can answer.</p> <p>12 A. I don't think so.</p> <p>13 Q. Well, if we go to --</p> <p>14 A. Coffee? Coffee?</p> <p>15 Q. Yes, that's what I said. Hot tea or</p> <p>16 hot coffee.</p> <p>17 A. They're talking about super heated.</p> <p>18 There are certain areas in the world where very</p> <p>19 hot beverages are consumed. It has nothing to do</p> <p>20 with what you do. Those very hot beverages can</p> <p>21 lead to cancer.</p> <p>22 Q. Sure. Very hot --</p> <p>23 A. Has nothing to do with your cup of</p> <p>24 coffee.</p> <p>25 Q. Very hot beverages --</p>
<p style="text-align: right;">Page 147</p> <p>1 A. It is, but you have to think about --</p> <p>2 you have to read the preamble and, you know, dose</p> <p>3 is part of the picture, so you have to take that</p> <p>4 into account. When they say something is group</p> <p>5 one, they're not talking -- they're not talking</p> <p>6 about dose specifically. They're not talking</p> <p>7 about other dose that you might get when you have</p> <p>8 bacon. They're saying that, you know, processed</p> <p>9 meat, consumption of processed meat can cause</p> <p>10 cancer in humans.</p> <p>11 Q. Sure.</p> <p>12 It's known to cause cancer in humans</p> <p>13 according to IARC?</p> <p>14 A. Yes, but they're not talking about</p> <p>15 the amount of processed meat. They don't do that.</p> <p>16 Q. Everything is dose dependent?</p> <p>17 MR. SLATER: Objection.</p> <p>18 You can answer.</p> <p>19 A. Most are. But, you know, the way you</p> <p>20 just stated this thing, it sounded like you</p> <p>21 weren't taking dose into account. The statement</p> <p>22 that, you know, that you made a couple minutes ago</p> <p>23 when you first brought up processed meat that --</p> <p>24 you said something like "The bacon that I enjoy</p> <p>25 for breakfast is a group one carcinogen." Yeah,</p>	<p style="text-align: right;">Page 149</p> <p>1 A. Not at all.</p> <p>2 Q. Very hot beverages above 65 degrees</p> <p>3 Celsius?</p> <p>4 A. I don't remember the temperature</p> <p>5 involved.</p> <p>6 Q. How does 65 --</p> <p>7 A. I think it's higher than that.</p> <p>8 Q. How does 65 degrees Celsius convert</p> <p>9 to Fahrenheit?</p> <p>10 A. Nine fifth C plus 32. You do the</p> <p>11 math.</p> <p>12 Q. I will.</p> <p>13 Are fried foods a known carcinogen</p> <p>14 according to IARC?</p> <p>15 A. Look on the list.</p> <p>16 Q. I'm asking you if you know. I will.</p> <p>17 But do you know?</p> <p>18 A. I haven't memorized the list. I told</p> <p>19 you that.</p> <p>20 MR. TRISCHLER: Go to page -- I'll</p> <p>21 come back to it because I can't find it right</p> <p>22 now.</p> <p>23 Q. Is it fair to say that according to</p> <p>24 IARC most of us are exposed to known and probably</p> <p>25 carcinogens on a daily basis?</p>

<p style="text-align: right;">Page 150</p> <p>1 A. I don't think IARC ever said that.</p> <p>2 I'm not aware that IARC ever made a statement like</p> <p>3 that.</p> <p>4 Q. Let me rephrase the question.</p> <p>5 Based on the IARC classifications of</p> <p>6 agents, would you agree that most of us are</p> <p>7 exposed to known and probable carcinogens on a</p> <p>8 daily basis?</p> <p>9 A. Well, we don't need IARC for that. I</p> <p>10 mean, you know, sunlight -- again, it's all in the</p> <p>11 dose. Everything is dependent on dose.</p> <p>12 Q. In our lifetime, all of us are going</p> <p>13 to be exposed to dozens of carcinogens; true?</p> <p>14 A. I wouldn't say necessarily dozens,</p> <p>15 but yes, we're all exposed to carcinogens, yes. I</p> <p>16 don't know about dozens. I don't know. I'm not</p> <p>17 sure what that means.</p> <p>18 Q. How about multiple? Would you agree</p> <p>19 that all of us during our lifetime are exposed to</p> <p>20 multiple carcinogens?</p> <p>21 A. Yes, multiple means more than one.</p> <p>22 Q. So when an individual has a lifetime</p> <p>23 exposure to multiple carcinogens, do you have the</p> <p>24 basis or ability to determine the cause of cancer</p> <p>25 in any individual case?</p>	<p style="text-align: right;">Page 152</p> <p>1 signature genetic lesion associated with NDMA?</p> <p>2 A. There is a signature genetic lesion,</p> <p>3 whether that would be associated with NDMA, but</p> <p>4 there might also be other causes. So</p> <p>5 O6-methylguanine is a signature genetic lesion, a</p> <p>6 mutation in the KRAS gene, G28 transition in the</p> <p>7 second base of codon 12. That's a signature that</p> <p>8 comes from O6-methylguanine. So yes, that's a</p> <p>9 signature mutation. Doesn't necessarily come from</p> <p>10 dimethylnitrosamine as opposed to perhaps another</p> <p>11 DNA methylating agent. We don't know. But that</p> <p>12 would be a signature mutation.</p> <p>13 Another example is in the P53 tumor</p> <p>14 suppressor gene where it's been shown that</p> <p>15 benzo(a)pyrene and some other polycyclic aromatic</p> <p>16 hydrocarbons as well as acrolein can cause</p> <p>17 mutations at certain specific codons of the P53</p> <p>18 tumor suppressor gene.</p> <p>19 Those would qualify as signature</p> <p>20 mutations. So yes, there are other examples other</p> <p>21 than the thymidine cross links that I mentioned</p> <p>22 earlier. So there are examples.</p> <p>23 Q. Maybe my question wasn't 100% clear.</p> <p>24 When I was using the term "signature</p> <p>25 genetic lesions," what I was referring to were</p>
<p style="text-align: right;">Page 151</p> <p>1 MR. SLATER: Objection.</p> <p>2 A. It's challenging. Definitely</p> <p>3 challenging, but there are examples. I think I</p> <p>4 mentioned one earlier where sunlight can cause a</p> <p>5 cross linking of thymidines in DNA in individuals</p> <p>6 who cannot repair that damage. It's a specific</p> <p>7 disease called xeroderma pigmentosa. Those</p> <p>8 individuals are exposed at all to sunlight, they</p> <p>9 get skin tumors. So yes.</p> <p>10 Q. Are you suggesting that -- it sounds</p> <p>11 like what you're suggesting is that sunlight can</p> <p>12 cause unique mutations?</p> <p>13 A. Yes.</p> <p>14 Q. Absent that example, when we talk</p> <p>15 about environmental exposures, do you have the</p> <p>16 ability to look at a given case and sort out</p> <p>17 multiple carcinogenic exposures and identify one</p> <p>18 as the cause of cancer in any given case?</p> <p>19 MR. SLATER: Objection.</p> <p>20 You can answer.</p> <p>21 A. Sure. An example would be smokeless</p> <p>22 tobacco. I can identify exposure to an oral</p> <p>23 cavity, oral mucosa carcinogen in smokeless</p> <p>24 tobacco.</p> <p>25 Q. Is there any such thing as a</p>	<p style="text-align: right;">Page 153</p> <p>1 lesions that would be unique to NDMA as opposed to</p> <p>2 other potential sources and it sounds like when</p> <p>3 you mentioned the P53 tumor, the O6-methylguanine</p> <p>4 and the KRAS gene, those lesions may be the</p> <p>5 result -- may be consistent with NDMA, but they</p> <p>6 might also be consistent with other causes?</p> <p>7 A. That's possible.</p> <p>8 Q. Right. So my question --</p> <p>9 A. But you know, everything has to be</p> <p>10 taken in context. So, you know, I think valsartan</p> <p>11 would be a good example of a study that could be</p> <p>12 done to identify such a genetic mutation that was</p> <p>13 caused by an NDMA.</p> <p>14 Q. But until that study is done, we</p> <p>15 can't say that the lesion is specifically caused</p> <p>16 by or related to DNA absent that scientific study?</p> <p>17 MR. SLATER: Objection.</p> <p>18 A. Related to what?</p> <p>19 Q. I misspoke. I'm sorry.</p> <p>20 Absent that study and until such a</p> <p>21 study is done, we don't have the scientific</p> <p>22 ability to look at a particular lesion and say it</p> <p>23 was definitively caused by NDMA exposure?</p> <p>24 MR. SLATER: Objection.</p> <p>25 You can answer.</p>

<p style="text-align: right;">Page 154</p> <p>1 A. No, not right now. We don't have the 2 data. The study should be done. 3 Q. I asked before about NDMA. 4 Are you aware of whether there's any 5 such thing as a signature genetic lesion 6 associated with NDEA? 7 A. NDEA would produce the same kind of 8 lesion in DNA O6-methylguanine, which could lead 9 to G2A transitions in codon 12. 10 Q. What is that -- 11 A. But I think there's less data for an 12 ethylating agent, but you would certainly expect 13 the same, the same thing. 14 Q. What is that opinion based on? 15 A. My knowledge of the scientific 16 literature. 17 Q. Is there scientific literature that 18 specifically describes the type of DNA changes 19 that one sees in humans from NDEA? 20 A. Not in humans. 21 Q. Following the discovery of 22 nitrosamines in some medications, you've been 23 involved in working with the FDA, correct? 24 A. Yes. 25 Q. One of the things you mentioned in</p>	<p style="text-align: right;">Page 156</p> <p>1 A. I really don't remember. I could dig 2 out the email if you really want to find out, if 3 you want me to. I don't remember the person's 4 name, but definitely they had contacted me. 5 They said there's going to be a 6 workshop on whatever the dates were and we're 7 planning the workshop and we'd like you to 8 participate as a panelist or discussant. I can 9 provide the email if you want. 10 Q. When you were approached by the FDA 11 to serve on this panel, did you disclose to them 12 your potential bias given your involvement in this 13 litigation? 14 MR. SLATER: Objection. 15 You can answer. 16 A. No, I don't believe I have a bias. I 17 don't have a bias. Definitely not. There's no 18 bias here. It's all based on science. 19 Q. All right. 20 A. I don't know why you bring up bias. 21 Q. Because I'm asking -- 22 A. Why would you do that? 23 Q. Because I'm asking questions, sir. 24 A. Okay. 25 Q. Did you disclose --</p>
<p style="text-align: right;">Page 155</p> <p>1 your report, and I think you alluded to it a 2 little bit earlier, is that you served as a 3 panelist in an FDA workshop in 2021, right? 4 A. Correct. 5 Q. I think that workshop was in March of 6 this year; true? 7 A. Yes. 8 Q. And at the time you attended that and 9 participated in that FDA workshop, you were an 10 active consultant for the plaintiffs in this 11 litigation; true? 12 A. Yes. 13 Q. You'd already been hired by 14 Mr. Slater over a year and a half ago? 15 A. Right. 16 Q. How did your involvement in this FDA 17 workshop come to be? 18 A. They contacted me and asked me 19 whether because of my extensive experience and 20 knowledge of nitrosamine carcinogenicity whether I 21 would like to participate. 22 Q. When you say they contacted you, are 23 you referring to someone at the FDA? 24 A. Yes. 25 Q. Who might that have been?</p>	<p style="text-align: right;">Page 157</p> <p>1 A. Okay. I'm saying I don't have any 2 bias. 3 Q. You said that six times, so let me 4 ask my next question. 5 A. So I want to make sure you understand 6 it. 7 Q. Did you disclose to the FDA that you 8 were working on behalf of the plaintiffs pursuing 9 claims against drug companies? 10 MR. SLATER: Objection. 11 You can answer. 12 A. I honestly don't remember. I may 13 have. I really don't remember. 14 Q. Do you have email correspondence 15 where you told them that? 16 A. I have email correspondence. Whether 17 I told them that or not, I really don't know. 18 Q. I think you were one of, like, 16 -- 19 A. I wouldn't consider it a conflict of 20 interest at all. 21 Q. I think you were one of, like, 16 22 members of this panel, right? 23 A. Yeah, that's right. 24 Q. Was it a group of esteemed experts in 25 their field?</p>

<p style="text-align: right;">Page 158</p> <p>1 A. Yes.</p> <p>2 Q. A group of well-respected scientists</p> <p>3 whose opinions you value and trust?</p> <p>4 A. Yes.</p> <p>5 Q. In addition to this workshop that you</p> <p>6 participated in with the FDA, were you also aware</p> <p>7 that the FDA has issued a number of public</p> <p>8 statements concerning the nitrosamine impurities</p> <p>9 found in drug products?</p> <p>10 A. Yes.</p> <p>11 Q. You've mentioned one of the things</p> <p>12 you did in your work in this case was to look into</p> <p>13 the public data and public information that was</p> <p>14 available on that, right?</p> <p>15 A. Yes.</p> <p>16 Q. So you were certainly aware that the</p> <p>17 FDA has made lots of public statements about the</p> <p>18 nitrosamine impurities and the significance of</p> <p>19 those impurities, correct?</p> <p>20 A. As well they should.</p> <p>21 Q. In those public statements, is it</p> <p>22 true that FDA has consistently observed and</p> <p>23 reported to the public that the theoretical risk</p> <p>24 of harm from nitrosamines in medications is</p> <p>25 extremely low?</p>	<p style="text-align: right;">Page 160</p> <p>1 for me?</p> <p>2 MR. TRISCHLER: Top of the page says</p> <p>3 "What you should know about nitrosamine</p> <p>4 impurities." It's the middle box. I'm</p> <p>5 sorry. There we go. Yes. Okay. Sorry.</p> <p>6 Different printing.</p> <p>7 Q. You can see in the middle of the</p> <p>8 page -- I think it's the fourth bullet point that</p> <p>9 we've expanded -- that reads "Nitrosamine</p> <p>10 impurities may increase the risk of cancer if</p> <p>11 people are exposed to them above acceptable levels</p> <p>12 and over long periods of time, but a person taking</p> <p>13 a dose that contains nitrosamines at or below</p> <p>14 acceptable daily intake limits every day for 70</p> <p>15 years is not expected to have an increased risk of</p> <p>16 cancer."</p> <p>17 Do you see that statement?</p> <p>18 A. Yes.</p> <p>19 Q. Do you agree with it, sir?</p> <p>20 A. Well, I thought that they had come</p> <p>21 out with a risk estimate. I've forgotten the</p> <p>22 exact number. So I'm a little confused by this</p> <p>23 particular statement. I'm not quite sure what</p> <p>24 they mean, "not expected to have an increased risk</p> <p>25 of cancer." It's a little confusing.</p>
<p style="text-align: right;">Page 159</p> <p>1 A. Yes.</p> <p>2 MR. TRISCHLER: For instance -- why</p> <p>3 don't we mark as Exhibit 11 this document</p> <p>4 entitled "Information about Nitrosamine</p> <p>5 Impurities in Medications" that comes from</p> <p>6 the FDA website?</p> <p>7 Can you mark that, Bill?</p> <p>8 THE VIDEOGRAPHER: Sure thing. Just</p> <p>9 looking for it now.</p> <p>10 (Whereupon, Exhibit 11 was marked for</p> <p>11 identification.)</p> <p>12 Q. What you're looking at now is an</p> <p>13 eight-page document from the FDA website.</p> <p>14 Is this one of the things you read --</p> <p>15 do you know if this was one of the things you read</p> <p>16 in connection with your work in this case?</p> <p>17 A. I don't recall this.</p> <p>18 Q. Can you go to page four of the</p> <p>19 exhibit, sir? The last section has a number of</p> <p>20 bullet points. Thank you.</p> <p>21 I don't know that this is page four</p> <p>22 that you have. At least it's not page four of</p> <p>23 mine.</p> <p>24 THE VIDEOGRAPHER: What are you</p> <p>25 looking for on the page? This is page four</p>	<p style="text-align: right;">Page 161</p> <p>1 Q. It seems to me what they're saying is</p> <p>2 at low levels, they would not expect nitrosamines</p> <p>3 in valsartan medications to cause an increased</p> <p>4 risk of cancer.</p> <p>5 Do you agree or disagree?</p> <p>6 MR. SLATER: Objection.</p> <p>7 You can answer.</p> <p>8 A. Well, I'm pretty sure they -- I don't</p> <p>9 know whether it was after this or -- I'm pretty</p> <p>10 sure they came out actually with a risk estimate</p> <p>11 of something like a one in 7,000 or something like</p> <p>12 that. So I don't know how that relates to this</p> <p>13 exactly, but I know that they -- their position</p> <p>14 was that the risk was low. So I'm aware of that.</p> <p>15 Q. Let's start with that.</p> <p>16 You said you're aware that the FDA's</p> <p>17 position that the risk of nitrosamines in</p> <p>18 valsartan-containing medications containing was</p> <p>19 low.</p> <p>20 Do you agree with that statement?</p> <p>21 MR. SLATER: Objection.</p> <p>22 You can answer.</p> <p>23 A. It was low compared to the benefit of</p> <p>24 the medication. So they recognize the fact that</p> <p>25 the medications are effective and that they are</p>

<p style="text-align: right;">Page 162</p> <p>1 useful drugs and as I understand it, their 2 position was that, you know, even though this 3 horrible contamination has happened and, you know, 4 it never should have happened, never would have 5 been approved in any way whatsoever, but these 6 drugs have been approved by FDA, if they had been 7 known to contain dimethyl and dimethylnitrosamine, 8 there's no way they would ever be approved, but 9 the fact that it did happen and the drugs are out 10 there now in the market, they were trying to tell 11 people that don't stop taking your drug right now 12 because, you know, that could have worse 13 consequences than the nitrosamines. That's how I 14 understand it. 15 MR. TRISCHLER: Object and move to 16 strike as non-responsive. 17 Q. Let's look at the sentence that's up 18 on the screen. 19 Do you agree with the statement that 20 a person taking a drug that contains nitrosamines 21 at or below the acceptable daily intake limits 22 every day for 70 years is not expected to have an 23 increased risk of cancer? 24 A. No. 25 Q. Do you realize that this statement</p>	<p style="text-align: right;">Page 164</p> <p>1 A. I'm not sure how to answer that. I 2 thought that they came up with a 96 nanograms per 3 day. That's what they came up with, that 4 96 nanograms per day would be acceptable. Above 5 that would not be. 6 Q. Right. That was my question. 7 Based on its risk assessment, the FDA 8 established that an acceptable daily intake of 9 NDMA was 96 nanograms per day. 10 You're familiar with that, right? 11 A. Yes, that's what I said. 12 Q. Based on FDA's risk assessment, it 13 was -- they determined an acceptable daily intake 14 of 26.5 nanograms per day was acceptable for NDEA, 15 right? 16 A. Yes. 17 Q. You understood that those acceptable 18 daily intake numbers were based on a lifetime 19 exposure of 70 years, correct? 20 A. Yes, that's how they did the 21 calculation. 22 Q. So if you do the math for NDMA, 96 23 times 365 times 70 leaves a lifetime acceptable 24 exposure limit, according to FDA, of 25 2.5 million nanograms, right, plus change?</p>
<p style="text-align: right;">Page 163</p> <p>1 was prepared after the FDA had done a risk 2 assessment on the relative risk presented by 3 nitrosamine impurities? 4 A. Yeah, I'm not sure exactly about this 5 statement -- okay? -- because I thought -- maybe 6 I'm wrong here, but as I recall, FDA actually came 7 out with a number based on a risk assessment 8 exercise that was something like, you know, one in 9 9,000 or something like that. So I'm a little 10 confused by this statement. I did not expect it. 11 I'm not sure what it means, not expected to have 12 an increased risk of cancer. 13 Q. Well, if the words -- 14 A. What does that mean exactly, "not 15 expected to"? I don't understand that. 16 Q. If the words "not expected" are 17 troubling to you, I'll withdraw the question. Let 18 me ask you something different. 19 Have you conducted an independent 20 risk assessment related to nitrosamine exposure 21 from valsartan-containing medications? 22 A. No, I have not. 23 Q. Do you understand that regulatory 24 limits for acceptable daily intake have been 25 established by FDA?</p>	<p style="text-align: right;">Page 165</p> <p>1 A. You did it, not me. 2 Q. A lifetime acceptable limit of NDEA 3 according to FDA's risk assessment would be 26.5 4 times 365 times 70, right? 5 A. Yes. 6 Q. And you understand, I assume, that no 7 plaintiff in this case was taking nitrosamines 8 containing -- nitrosamine-containing medications 9 for 70 years or anything close to that, right? 10 A. Probably not. 11 Q. And what FDA said in its risk 12 assessment was that exposure to roughly two and a 13 half million nanograms of NDMA was reasonably safe 14 for human consumption, right? 15 A. Yes. 16 Q. That's what a risk assessment is? 17 A. Yes. 18 Q. Do you agree with that risk 19 assessment? 20 A. Yes, I agree with it. I mean, it's 21 not really my area. I don't present myself as an 22 expert in risk assessment or the calculation of 23 risk. I don't do that. But I think it's 24 reasonable what they did, what they came up with. 25 It sounds reasonable to me.</p>

<p style="text-align: right;">Page 166</p> <p>1 Q. But you do suggest, at least through 2 your report, that you believe that nitrosamines in 3 valsartan-containing medication increase the risk 4 of causing cancer, right? 5 A. Yes, absolutely. 6 Q. And you told me that everything is 7 dose and duration dependent, right? 8 A. Yes. 9 MR. SLATER: Objection. 10 Q. So you need to know if you're going 11 to have an opinion that an exposure increased the 12 risk of causing cancer, you need to know what a 13 reasonably safe level for human consumption is, 14 right? 15 MR. SLATER: Objection. 16 You can answer. 17 A. The safe level is zero. That's what 18 it should be. 19 Q. That's not what -- not according to 20 the FDA. 21 A. Well, that's okay. There's no way 22 there should be NDMA or NDEA in these drugs. It 23 should be zero. Absolutely. 24 MR. TRISCHLER: Object and move to 25 strike because those are issues for another</p>	<p style="text-align: right;">Page 168</p> <p>1 risk calculation? 2 A. No. 3 MR. SLATER: Objection. 4 Lack of foundation. 5 Q. That conference was over the course 6 of two days, correct? 7 A. Yes. 8 Q. So if you had disagreement with FDA's 9 risk calculation, you certainly had plenty of time 10 to offer it, right? 11 MR. SLATER: Objection. 12 A. Sure, but as I recall -- I don't 13 really remember. I don't think the -- this 14 particular -- I don't remember whether, you know, 15 the risk calculation was actually discussed at the 16 workshop. I really don't remember. 17 Q. Well, certainly -- 18 A. The workshop wasn't specifically -- 19 it was more general -- about nitrosamine exposure 20 and carcinogenicity. Obviously, it related to 21 drugs because that's what they do, but I don't 22 really remember whether the risk calculation was 23 actually discussed at that workshop. I don't 24 think it was. 25 Q. Well, you've already told me that you</p>
<p style="text-align: right;">Page 167</p> <p>1 day, sir. 2 We're talking about causation here. 3 MR. SLATER: Objection. 4 Argumentative. 5 Q. Excuse me. 6 What the FDA said is that two and a 7 half million nanograms of NDMA are reasonably safe 8 for human consumption based on its risk assessment 9 and you've not done any other assessment to say 10 otherwise; true? 11 MR. SLATER: Objection. 12 Lack of foundation. 13 You can answer. 14 A. It's not what I do. That's true. I 15 haven't done -- I haven't made any calculations. 16 That's up to FDA, EMA and the risk assessors. 17 That's not what I do. 18 Q. What the FDA has said is that 19 677,075 nanograms of NDEA is reasonably safe for 20 human consumption and you've not done any 21 alternative risk assessment to suggest otherwise? 22 A. Correct. 23 Q. When you sat in on the FDA 24 nitrosamine workshop in March of this year, did 25 you publically express any disagreement with FDA's</p>	<p style="text-align: right;">Page 169</p> <p>1 are aware that the FDA, as the agency responsible 2 for drug safety in America, has repeatedly made 3 public statements that the health risk from 4 nitrosamine impurities was very low. 5 Do you remember telling me that? 6 A. Yes. 7 Q. And the workshop that you attended in 8 March, there was actually a transcript prepared of 9 the whole thing. 10 Were you aware of that? 11 A. Yes, I'm aware. 12 Q. Do you have a copy of the transcript? 13 A. No. Well, it might be on my 14 computer. I don't have a hard copy. Not here 15 with me, no. 16 Q. Have you ever reviewed a transcript 17 of the FDA workshop when you came back after it 18 was completed in March? 19 A. I did review it, yes. 20 Q. And it was certainly discussed during 21 the workshop, on multiple occasions, the fact that 22 the risk from exposure to nitrosamine in 23 valsartan-containing medications was de minimis. 24 That was clearly discussed, correct? 25 MR. SLATER: Objection.</p>

<p style="text-align: right;">Page 170</p> <p>1 You can answer.</p> <p>2 A. Yes.</p> <p>3 Q. When you were sitting there for two</p> <p>4 days, did you ever express to anyone on that panel</p> <p>5 your disagreement with that belief?</p> <p>6 A. No.</p> <p>7 Q. Did you tell anyone that FDA during</p> <p>8 this two-day panel that they were wrong, that the</p> <p>9 risk of developing cancer from these small amounts</p> <p>10 of nitrosamines was actually much larger than that</p> <p>11 they believed?</p> <p>12 MR. SLATER: Objection.</p> <p>13 You can answer.</p> <p>14 A. No, I told you that's not what I do.</p> <p>15 I don't do risk assessment calculations, so I</p> <p>16 would have no grounds to do that, to say that and</p> <p>17 I'm not disagreeing with the risk assessment</p> <p>18 calculations that are out there.</p> <p>19 Q. Okay.</p> <p>20 A. That's not what I do, so why would I</p> <p>21 say something like that?</p> <p>22 Q. My point is that you had an</p> <p>23 opportunity in March to tell the FDA that their</p> <p>24 assessment of the risk of nitrosamine impurities</p> <p>25 in drugs being anything but de minimis was wrong</p>	<p style="text-align: right;">Page 172</p> <p>1 that actually asks that question?</p> <p>2 I'll be happy to wait for you to look</p> <p>3 for that in the transcript.</p> <p>4 Q. Did you tell anyone at FDA their risk</p> <p>5 assessment was wrong? Yes or no?</p> <p>6 A. No.</p> <p>7 Q. Although you don't -- although you</p> <p>8 say risk assessments are not your business, are</p> <p>9 you aware of the fact that risk assessments, when</p> <p>10 they're performed by regulatory agencies, are</p> <p>11 intended to be extremely conservative so as to</p> <p>12 decide a patient's safety?</p> <p>13 A. Yes.</p> <p>14 Q. Would you agree that the</p> <p>15 establishment of a conservative, acceptable intake</p> <p>16 limit does not imply that an exposure at a higher</p> <p>17 level can cause harm?</p> <p>18 MR. SLATER: Objection.</p> <p>19 A. I'm not sure I understand your</p> <p>20 question.</p> <p>21 Q. Based on what you know about risk</p> <p>22 assessments, would you agree that it is generally</p> <p>23 known and understood that those -- the</p> <p>24 establishment of those conservative estimates does</p> <p>25 not mean that an exposure at levels above what's</p>
<p style="text-align: right;">Page 171</p> <p>1 and you did nothing about it.</p> <p>2 Agreed?</p> <p>3 MR. SLATER: Objection.</p> <p>4 Lack of foundation.</p> <p>5 Complete mischaracterization of what</p> <p>6 went on.</p> <p>7 You can answer.</p> <p>8 A. I think I already told you, I don't</p> <p>9 do risk assessment, so, you know, I wouldn't argue</p> <p>10 with the FDA's risk calculation. I already told</p> <p>11 you that, so why do you keep asking?</p> <p>12 Q. I'm trying to get an answer to my</p> <p>13 question.</p> <p>14 Did you tell anyone at FDA --</p> <p>15 MR. SLATER: Counsel, one second.</p> <p>16 Counsel, he's answered the question</p> <p>17 multiple times. You're beyond the point of</p> <p>18 arguing with him.</p> <p>19 Is there some other area you want to</p> <p>20 ask him questions about --</p> <p>21 Q. Did you tell anybody --</p> <p>22 MR. SLATER: -- or do you want to</p> <p>23 pull the transcript out or show us the</p> <p>24 question or do you want to pull the</p> <p>25 transcript out and try to find a question</p>	<p style="text-align: right;">Page 173</p> <p>1 determined to be an acceptable level will</p> <p>2 necessarily cause harm?</p> <p>3 MR. SLATER: Objection.</p> <p>4 You can answer.</p> <p>5 A. Correct. It's based on the</p> <p>6 probability.</p> <p>7 Q. And in fact --</p> <p>8 A. It's all based on probability</p> <p>9 calculations.</p> <p>10 Q. In fact, in some of the research that</p> <p>11 you cited in your report that you prepared in this</p> <p>12 case, you identified evidence and provided us with</p> <p>13 information suggesting that virtually all of us</p> <p>14 are exposed to NDMA and NDEA on a daily basis at</p> <p>15 concentrations far greater than the acceptable</p> <p>16 intakes established by FDA, right?</p> <p>17 A. I don't know about "far greater." We</p> <p>18 are all exposed through the diet for sure.</p> <p>19 Q. Okay.</p> <p>20 A. I don't know about "far greater."</p> <p>21 That depends on your diet, that depends on</p> <p>22 concentrations of NDMA and NDEA and the various</p> <p>23 foods that you eat and drinking water, etc. So I</p> <p>24 don't know about "far greater."</p> <p>25 (Whereupon, Exhibit 12 was marked for</p>

<p style="text-align: right;">Page 174</p> <p>1 identification.)</p> <p>2 Q. Let's take a look at the paper that</p> <p>3 you cited in your report from Gushgari,</p> <p>4 G-U-S-H-G-A-R-I. I think it's entitled "Critical</p> <p>5 Review of Major Sources of Human Exposure to</p> <p>6 Nitrosamines."</p> <p>7 Do you recall this paper, Dr. Hecht?</p> <p>8 A. Yes.</p> <p>9 Q. Was my representation correct, that</p> <p>10 this was indeed a paper that you cited in your</p> <p>11 report that you prepared in this case?</p> <p>12 A. It is, yes.</p> <p>13 Q. And in Gushgari, the authors</p> <p>14 concluded that some Americans ingest as much as</p> <p>15 25,000 to 30,000 nanograms of nitrosamines every</p> <p>16 single day, correct?</p> <p>17 A. That's with respect to tobacco use, I</p> <p>18 believe.</p> <p>19 Q. Right.</p> <p>20 So smokers, according to Gushgari,</p> <p>21 consume on the order of 25,000 to 30,000 nanograms</p> <p>22 of nitrosamines every day?</p> <p>23 A. I'm not sure whether he means smokers</p> <p>24 or smokeless tobacco users. I'd have to look at</p> <p>25 that.</p>	<p style="text-align: right;">Page 176</p> <p>1 Q. And what he said was that if you --</p> <p>2 if tobacco use -- if you're a smoker, the rate of</p> <p>3 your nitrosamine intake is on the order of 21,800</p> <p>4 plus or minus 4,350 nanograms per day, right?</p> <p>5 A. I don't think it also includes</p> <p>6 smokers. I think it's smokeless tobacco users.</p> <p>7 Q. Understood.</p> <p>8 But what he discusses in this paper</p> <p>9 is that in addition to tobacco, our diet is also a</p> <p>10 source of nitrosamines, correct?</p> <p>11 A. Correct.</p> <p>12 Q. According to Gushgari, depending on</p> <p>13 what you eat, you'll consume between 1,800 to</p> <p>14 1,900 nanograms of nitrosamine from your food,</p> <p>15 right?</p> <p>16 A. That's what he came up with, right.</p> <p>17 Q. Beer was another -- if you go to page</p> <p>18 1131, I think beer was also a source of -- or</p> <p>19 potential source -- of nitrosamines according to</p> <p>20 Gushgari on the order of 1,000 nanograms per day,</p> <p>21 right?</p> <p>22 A. Mm-hmm. Yeah.</p> <p>23 Q. He also noted that water was a source</p> <p>24 of nitrosamines on the order of about</p> <p>25 120 nanograms per day?</p>
<p style="text-align: right;">Page 175</p> <p>1 Q. Okay.</p> <p>2 A. Then you know there's the question of</p> <p>3 whether it's nitrosamines in general or</p> <p>4 specifically tobacco specific nitrosamines</p> <p>5 or dimethylnitrosamine. I'd have to go back and</p> <p>6 look at that. So I'm not sure about that number</p> <p>7 you just gave me.</p> <p>8 Q. Well, let's go --</p> <p>9 A. Because the levels of</p> <p>10 dimethylnitrosamine in a cigarette are actually</p> <p>11 quite low.</p> <p>12 Q. Well, you can certainly --</p> <p>13 A. He was talking about nitrosamines in</p> <p>14 general, so that would include tobacco specific</p> <p>15 nitrosamines, which are present in higher</p> <p>16 concentrations. So I think that's where he got</p> <p>17 the tobacco part in his pie chart or whatever it</p> <p>18 was.</p> <p>19 Q. Let's go to page 1130 of this Exhibit</p> <p>20 number 12, please. It's the last paragraph on the</p> <p>21 right-hand side.</p> <p>22 One of the things Dr. Gushgari did</p> <p>23 was to estimate nitrosamine intake and nitrosamine</p> <p>24 exposure for all of us, correct?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">Page 177</p> <p>1 A. Yeah, I don't know if that's -- I'm</p> <p>2 not sure about that number. Water is very low.</p> <p>3 Q. It says -- it was highlighted.</p> <p>4 Can you highlight it again, please?</p> <p>5 According to the paper here, the</p> <p>6 nitrosamine exposure from water is about</p> <p>7 120 nanograms per day, right?</p> <p>8 A. Yeah, but I'm not sure -- there's</p> <p>9 some problems with -- there's some measurement</p> <p>10 problems with the order story having to do with</p> <p>11 artifact formation of NDMA during analysis. So</p> <p>12 I'm not sure. I don't recall whether his water</p> <p>13 calculation I think was -- may have been carried</p> <p>14 out before some of those analytical chemistry</p> <p>15 problems came to light. So I'm not sure about the</p> <p>16 water. I have to look at that more carefully.</p> <p>17 Q. This study was done in 2018, right?</p> <p>18 A. The review was published in 2018.</p> <p>19 Q. Correct.</p> <p>20 A. I don't know whether all of the water</p> <p>21 literature that he considered was before the</p> <p>22 finding that some of the water measurements were</p> <p>23 wrong. I don't know offhand.</p> <p>24 Q. So what you're suggesting to me --</p> <p>25 what you're suggesting to me --</p>

<p style="text-align: right;">Page 178</p> <p>1 A. I'm suggesting that the water might 2 be wrong. Everything else probably right. 3 Q. Might be lower than 120 nanograms? 4 A. Right. Yeah. 5 Q. I guess it would depend on the 6 quality of the water you drink, where you get it, 7 what the source is, right? 8 A. In part, but, I mean, the calculation 9 would have to be redone based on the actual data. 10 That's not -- that doesn't have artifacts in it. 11 Q. Well, so let's take water out of the 12 equation because you said the other numbers from 13 Gushgari are probably right. 14 So what his paper suggests to us is 15 that individuals who are exposed to tobacco will 16 consume around 25,000 nanograms of nitrosamines 17 every single day of their life, right? 18 A. No, not exposed to tobacco. Use 19 tobacco. There's a difference. 20 Q. Individuals who use tobacco will be 21 exposed to 25,000 nanograms of nitrosamine every 22 day, right? 23 A. That's what he came up with, yes. 24 Q. For those non-smokers and 25 non-drinkers who lead a good, healthy life,</p>	<p style="text-align: right;">Page 180</p> <p>1 identified for you before as a company that I'm 2 representing. You heard of that name before and 3 you reviewed some of their data, correct? 4 A. Yes. 5 Q. If I could just direct your attention 6 just for a second to -- I think it's page 24 and 7 25 of your report. 8 One of the things you indicate on 9 pages 24 and 25 of your report is you had the 10 opportunity to review information relating to 11 nitrosamine levels that were observed in Mylan 12 product, right? 13 A. Yes. 14 Q. On page 25, the first full paragraph, 15 you write that Mylan's API testing confirmed NDEA 16 levels in API batches ranging from 0.1 parts per 17 million to 1.57 parts per million. 18 Did I read that accurately from your 19 report? 20 A. Yes. 21 Q. As part of your work in this case, 22 sir, did you take that data and attempt to 23 calculate a mean NDEA concentration for Mylan's 24 valsartan? 25 A. No, I did not.</p>
<p style="text-align: right;">Page 179</p> <p>1 according to Gushgari, those individuals are going 2 to be exposed to daily levels of nitrosamines on 3 the order of about 2,000 nanograms per day, right? 4 A. From food. Food and water, I guess, 5 and beer. I don't know. The 2,000 is just from 6 food or is it 2,000 from food plus beer plus 7 water? 8 Q. Beer is separate. That's why I left 9 it out. 10 A. Yeah. So what is it just from food? 11 Q. It says -- right in the first line 12 that you're looking at here on the exhibit, 1,800 13 plus or minus 350 for a vegetarian diet, 1,900 14 plus or minus 380 for a Western diet. 15 A. Okay. 16 Q. So I was using 2,000 as a round 17 number. 18 A. Okay. 19 Q. In your report, you suggest that you 20 received information about nitrosamine levels 21 observed in the valsartan-containing products of 22 some of the defendants to this litigation, 23 correct? 24 A. Yes. 25 Q. One of the defendants is Mylan, who I</p>	<p style="text-align: right;">Page 181</p> <p>1 Q. I'll represent to you that the mean 2 is 0.47 parts per million for all batches tested 3 and I'll ask you to accept that number for 4 purposes of my next question. 5 Okay? 6 A. Okay. 7 MR. SLATER: Objection. 8 You can answer. 9 Q. If you know the parts per million of 10 a nitrosamine, you can convert that to nanograms 11 by multiplying it by the dose, right? 12 A. Yes. 13 Q. In fact, you've done -- you did that 14 calculation in various parts of your report? 15 A. Yes. 16 Q. So if we assume an NDEA concentration 17 at the mean of 0.47 parts per million and multiply 18 it by the highest possible dose, 300 micrograms of 19 valsartan, we get a nanogram of about 20 150 nanograms per day, correct? 21 A. Okay. 22 Q. 0.47 times 320? 23 A. Okay. 24 Q. Do you agree that that math comes out 25 to about 150?</p>

<p style="text-align: right;">Page 182</p> <p>1 A. Sounds right, yeah.</p> <p>2 Q. So taking the mean from my data of</p> <p>3 about 0.47, what it tells us is that</p> <p>4 hypothetically, a user of Mylan's valsartan may</p> <p>5 have consumed an additional 150 nanograms per day</p> <p>6 during the period he or she used the drug, right?</p> <p>7 A. Right. Yes.</p> <p>8 Q. So if we go back then to Gushgari's</p> <p>9 numbers, we know that tobacco users have a daily</p> <p>10 nitrosamine intake on the order of</p> <p>11 25,000 nanograms, correct?</p> <p>12 A. Is that his number?</p> <p>13 Q. For tobacco users.</p> <p>14 A. Yes.</p> <p>15 Q. If we assume an intake now of</p> <p>16 150 nanograms a day for Mylan's valsartan, that</p> <p>17 individual has increased their daily nitrosamine</p> <p>18 intake by a scant 0.6%, right?</p> <p>19 A. Correct.</p> <p>20 Q. If we take a non-smoker and a</p> <p>21 non-drinker who is living right, Gushgari tells us</p> <p>22 they will have exogenously consumed about 2,000</p> <p>23 nanograms a day.</p> <p>24 Do you see that highlighted?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">Page 184</p> <p>1 even advanced enough that the worldwide agencies</p> <p>2 classify NDEA or NDMA as known human carcinogens,</p> <p>3 right? They've never done that?</p> <p>4 A. Well, I wouldn't say that exactly</p> <p>5 because -- go back to my book here. It says that</p> <p>6 it should be regarded for practical purposes as if</p> <p>7 it were carcinogenic to humans, 1978. 1978, but</p> <p>8 you're right.</p> <p>9 Q. Right about what?</p> <p>10 A. No one has said that 7.5% increase in</p> <p>11 nitrosamine exposure would lead to cancers in</p> <p>12 humans --</p> <p>13 Q. I think it's one o'clock --</p> <p>14 A. -- in the setting that you just</p> <p>15 described.</p> <p>16 Q. I think it's one o'clock. I'm</p> <p>17 willing to keep going, but you had indicated you</p> <p>18 wanted to take a break at one o'clock, Doctor.</p> <p>19 Do you want to --</p> <p>20 A. My watch says 12:30.</p> <p>21 Q. Okay. Let's keep going.</p> <p>22 A. It's 12:30 here.</p> <p>23 Q. Sorry. Let's keep going then.</p> <p>24 So what we've been talking about so</p> <p>25 far is that exogenous nitrosamine consumption,</p>
<p style="text-align: right;">Page 183</p> <p>1 Q. If we assume an intake of 150</p> <p>2 nanograms per day for Mylan's valsartan, that</p> <p>3 clean-living individual has increased his or her</p> <p>4 nitrosamine intake by about 7.5%, right?</p> <p>5 A. Correct.</p> <p>6 Q. So what I'd like to know, Dr. Hecht,</p> <p>7 is what peer-reviewed scientific literature has</p> <p>8 ever been published to suggest that a modest one</p> <p>9 to seven percent increase in nitrosamine</p> <p>10 concentrations over a limited period of time would</p> <p>11 cause cancer in humans?</p> <p>12 A. I'm not aware of any.</p> <p>13 Q. In your report, you certainly don't</p> <p>14 cite any research or studies that establish a one</p> <p>15 to seven percent increase in baseline nitrosamine</p> <p>16 consumption will lead to cancer in humans.</p> <p>17 Do you?</p> <p>18 MR. SLATER: Objection.</p> <p>19 A. No.</p> <p>20 Q. And you don't cite any because no</p> <p>21 such data exists, right?</p> <p>22 A. I didn't cite any. So if it existed,</p> <p>23 I would have cited it.</p> <p>24 Q. Right.</p> <p>25 And the fact is that science hasn't</p>	<p style="text-align: right;">Page 185</p> <p>1 correct?</p> <p>2 A. Yes.</p> <p>3 Q. And when we talk about exogenous</p> <p>4 consumption, we mean nitrosamines formed outside</p> <p>5 the organism, right?</p> <p>6 A. Yes.</p> <p>7 Q. In this case, though, with respect to</p> <p>8 nitrosamines like NDMA and NDEA, we know that</p> <p>9 they're also formed endogenously, right?</p> <p>10 A. No, we don't really know that. We</p> <p>11 don't know that NDMA and NDEA are formed</p> <p>12 endogenously. We don't know that.</p> <p>13 Q. Huh. Well, have you seen research</p> <p>14 suggesting that endogenous formation of NDEA and</p> <p>15 NDMA and other nitrosamines are significant?</p> <p>16 A. Yes, I have seen such research and I</p> <p>17 believe it's wrong.</p> <p>18 Q. Well, tell me what research you've</p> <p>19 seen to suggest that NDMA and NDEA are not formed</p> <p>20 endogenously.</p> <p>21 A. I don't think that it's -- let's put</p> <p>22 it this way: It's hard to prove a negative. I</p> <p>23 can't cite any research that proves that they're</p> <p>24 not formed endogenously. We do know that there's</p> <p>25 very solid research that some nitroso compounds</p>

<p style="text-align: right;">Page 186</p> <p>1 are formed endogenously. These are nitrosamines 2 such as nitrosoproline that are not metabolized, 3 so we can actually track their formation in humans 4 by measuring them in urine because they're not 5 metabolized. 6 But NDMA and NDEA present a different 7 problem because they are metabolized, so it's very 8 difficult to track their formation in humans. 9 So the endogenous formation of NDMA 10 and NDEA is very challenging. It's very 11 challenging to establish and I don't believe that 12 it's been established. 13 Q. Well, I agree with you that it's 14 challenging. I may agree with you that it's not 15 been firmly established, but I think the statement 16 you made earlier that's causing me some 17 consternation is I believe you said that you do 18 not believe and you are of the opinion that there 19 is no endogenous formation of NDMA. 20 Is that an opinion you intend to 21 offer in this case? 22 MR. SLATER: Objection. 23 You can answer. 24 A. No, I don't think I said that or if I 25 did say that, it's wrong. What I did say is that</p>	<p style="text-align: right;">Page 188</p> <p>1 that there are studies out there that claim 2 endogenous formation of NDMA and NDEA does occur. 3 I think it's NDMA mainly. But I believe some of 4 the methods in those studies are flawed. That's 5 what I said. 6 Q. Is it true that the FDA has 7 publically stated that the amount of endogenous 8 formation of carcinogenic nitrosamines such as 9 NDMA and NDEA is unknown? 10 A. I believe that's true. I think that 11 was one of the conclusions of the workshop. 12 Q. Sure. And one of the conclusions of 13 the workshop was that no scientist could say 14 whether the amount of endogenous formation was 15 equal to, less than or greater than our exogenous 16 intake of those nitrosamines? 17 A. Yes, that's right. We don't know. 18 Q. So for all we know, if Gushgari's 19 estimates of endogenous intake of a non -- 20 A. Exogenous. Exogenous. 21 Q. Let me start over. 22 A. Gushgari estimated exogenous intake. 23 Q. Okay. I'm going to try again. 24 For all we know, if we use Gushgari's 25 estimate of exogenous intake of 2,000 nanograms</p>
<p style="text-align: right;">Page 187</p> <p>1 in my opinion, there's no solid evidence for 2 endogenous formation of NDMA and NDEA in humans. 3 There are studies out there, but I believe that 4 they're flawed. 5 Q. You are not aware of any study 6 suggesting or concluding that NDMA does not form 7 endogenously; true? 8 A. I'm not aware of any study that it 9 doesn't form endogenously? Is that what you're 10 asking? It's a double negative. Can you clarify? 11 Q. I'll rephrase it. 12 Are there any studies to your 13 knowledge that conclude that there is no such 14 thing has endogenous formation of NDMA? 15 A. No. 16 Q. Are you aware of any studies 17 suggesting there's no such thing as endogenous 18 formation of NDEA? 19 A. No. 20 Q. You're not going to offer the opinion 21 in a courtroom in America suggesting that 22 endogenous formation of NDMA or NDEA does not 23 occur? 24 A. That's correct. I didn't say that. 25 I never said that. In fact, what I did say was</p>	<p style="text-align: right;">Page 189</p> <p>1 per day for a non-tobacco user, endogenous NDMA 2 formation could be 2,000 nanograms, could be 3 1,000, could be 3,000 nanograms per day, right? 4 A. Right. We don't know. 5 Q. We don't know. 6 A. Right. 7 Q. Let's just assume that it's -- that 8 endogenous formation and exogenous formation are 9 equal to one another. 10 A. Why would you assume that? 11 Q. I'm going to ask you hypothetically 12 to assume. 13 What that would suggest to us is that 14 any nitrosamine intake for an individual who was 15 taking valsartan-containing medications subject to 16 a recall would be at an even lower percentage than 17 if you had considered simply exogenous intake? 18 MR. SLATER: Objection. 19 A. Yes. Sure. If there's also 20 endogenous formation, then the amount from the 21 drug on a percentage basis obviously would be 22 less. 23 Q. Right. 24 So we used Gushgari's estimates for 25 the mean Mylan exposure and determined it to be</p>

<p style="text-align: right;">Page 190</p> <p>1 0.6% to 7.5%. If we assume endogenous formation, 2 those percentages go down. 3 A. Correct. 4 Q. How much they go down is unknown 5 because, according to you, the scientific 6 community doesn't know how much endogenous 7 formation of nitrosamines takes place? 8 A. I don't think it's just according to 9 me, but yes, that's true. 10 Q. Well, I say that because you're the 11 only person I'm asking today. 12 A. Okay. 13 Q. You've indicated that the level of 14 endogenous formation of nitrosamines is unknown, 15 that there are scientists who have published peer 16 reviewed papers suggesting that endogenous 17 formation is quite high and far exceeds our intake 18 exogenously? 19 A. Yes. 20 Q. One of those people was Gushgari, the 21 guy you cited in your report, right? 22 A. Yes. 23 MR. TRISCHLER: Can you put up page 24 1133 of this paper? Right where you have the 25 cursor, that paragraph right there happens to</p>	<p style="text-align: right;">Page 192</p> <p>1 A. Yes, I see it. 2 Q. So if Gushgari is right, that 3 clean-living individual we've been talking about 4 who takes in 2,000 nanograms per day of 5 nitrosamines endogenously -- or exogenously is 6 getting the other 197,000 endogenously, right? 7 MR. SLATER: Objection. 8 You can answer. 9 A. This is all wrong. I mean, this is 10 crazy because he's talking nitrosamines as a 11 class. So I mean what he's basing this on is 12 nitrosoproline, which is a noncarcinogenic, 13 non-metabolized nitrosamine that's been used as a 14 monitor for endogenous formation. I'm sure that's 15 what that calculation comes from. It had nothing 16 to do with dimethylnitrosamine because 17 nitrosoproline and the other nitroso amino acids 18 he's talking about are noncarcinogenic. 19 Q. Where does it say here that he's 20 talking about noncarcinogenic -- 21 A. I don't think it does. I'm sure 22 that's what he's talking about. 23 Q. Did you ask him? 24 A. No, I didn't ask him. 25 Q. How are you sure that's what he's</p>
<p style="text-align: right;">Page 191</p> <p>1 be the one I wanted to talk to the Doctor 2 about. 3 Q. About halfway through that -- when's 4 the last time you read this article, sir? 5 A. When was the last time I read it? 6 Q. Yes, sir. 7 A. Probably couple months ago. 8 Q. Fair to say you've read it a couple 9 times since you wrote your report? 10 A. I don't really know. 11 Q. But you certainly would have read it 12 before you wrote your report? 13 A. Yes, I did. 14 Q. While you cited to Gushgari in your 15 report, you did not cite to any problems or 16 limitations or disagreements that you had with his 17 conclusions or analysis, right? 18 A. Oh, yeah. That's true. 19 Q. What Gushgari says here, about 20 halfway through that paragraph that we've 21 highlighted, he says "Recent literature suggests 22 endogenous formation of nitrosamines governs human 23 exposure to these compounds that may account for 24 97% of the total nitrosamine load." 25 Do you see that?</p>	<p style="text-align: right;">Page 193</p> <p>1 talking about then -- 2 A. Because I know the literature. 3 Q. You have to let me finish the 4 question, sir. 5 A. You asked me how I knew. I said 6 because I know the literature. 7 Q. So where did Gushgari ever state that 8 his determination that endogenous formation of 9 nitrosamines applies only to those noncarcinogenic 10 nitrosamines and not nitrosamines thought to be 11 carcinogenic? 12 A. Thought to be carcinogenic? I don't 13 know. I can't speak for Gushgari. 14 Q. We talked before about the fact that 15 there were 300 plus nitrosamines that have been 16 identified in the scientific community. 17 How many are carcinogenic? 18 A. Most of them. The great majority. 19 It's not 300 nitrosamines. It's 300 nitroso 20 compounds. Not all nitroso compounds are 21 nitrosamines. I think the number for nitrosamines 22 is probably closer to 150 to 200. 23 Anyhow, that's besides the point. 24 What was your question? How many are 25 carcinogenic?</p>

<p style="text-align: right;">Page 194</p> <p>1 The great majority, but not -- not</p> <p>2 the ones that we have data on for endogenous</p> <p>3 formation. Those are noncarcinogenic.</p> <p>4 Nitrosoproline and some related nitros amino</p> <p>5 acids, that's where all the reliable endogenous</p> <p>6 formation data comes from and those compounds are</p> <p>7 noncarcinogenic because they're not metabolized.</p> <p>8 They're excreted unchanged because they're polar.</p> <p>9 Q. Did you finish your answer?</p> <p>10 A. Yes.</p> <p>11 Q. Endogenous formation of nitrosamines</p> <p>12 can occur with both nitrosamines that are</p> <p>13 carcinogenic and those that are thought to be</p> <p>14 noncarcinogenic, correct?</p> <p>15 A. Yes.</p> <p>16 Q. Have you don't any independent</p> <p>17 scientific research to quantify the levels of</p> <p>18 nitrosamines --</p> <p>19 Strike that.</p> <p>20 Have you done any independent</p> <p>21 scientific research to quantify the levels of NDMA</p> <p>22 that are formed endogenously?</p> <p>23 A. No. We have not done that.</p> <p>24 Q. Have you done any independent</p> <p>25 scientific research to quantify the levels of NDEA</p>	<p style="text-align: right;">Page 196</p> <p>1 MR. SLATER: Objection.</p> <p>2 A. Of total nitrosamines, including the</p> <p>3 noncarcinogenic ones --</p> <p>4 Q. Just those two is my question.</p> <p>5 A. So you're saying -- you start the</p> <p>6 question or sentence -- whatever it was -- with</p> <p>7 NDMA and NDEA and you end the thought -- it's very</p> <p>8 confusing the way you said it. I mean, you have</p> <p>9 to be more specific.</p> <p>10 Q. I was --</p> <p>11 A. What we're talking about here is NDMA</p> <p>12 and NDEA.</p> <p>13 Q. I agree.</p> <p>14 In fairness, you didn't --</p> <p>15 A. The exposure to those is only a</p> <p>16 fraction of the total nitrosamine formation, which</p> <p>17 includes the noncarcinogenic nitrosamines. We</p> <p>18 don't know whether there's NDMA and NDEA formed</p> <p>19 endogenously.</p> <p>20 Q. Well, we do know there --</p> <p>21 A. That's a research question.</p> <p>22 Q. We do know there's NDMA in food?</p> <p>23 A. Yes.</p> <p>24 Q. We do know there's NDMA in beer?</p> <p>25 A. Yes.</p>
<p style="text-align: right;">Page 195</p> <p>1 that are formed endogenously?</p> <p>2 A. No.</p> <p>3 Q. Would you agree that evaluating --</p> <p>4 would you agree that in evaluating the issue of</p> <p>5 whether NDMA or NDEA actually caused cancer in</p> <p>6 humans, we need to consider that nitrosamines form</p> <p>7 both endogenously and exogenously?</p> <p>8 A. Yes.</p> <p>9 Q. And any intake of NDMA or NDEA from</p> <p>10 valsartan-containing medication would be just a</p> <p>11 fraction of an individual's nitrosamine load,</p> <p>12 correct?</p> <p>13 MR. SLATER: Objection.</p> <p>14 A. That's a very poorly phrased</p> <p>15 question, Counselor, I have to say because, again,</p> <p>16 you're mixing carcinogenic nitrosamines --</p> <p>17 highly-carcinogenic nitrosamines, like NDMA and</p> <p>18 NDEA, with noncarcinogenic nitrosamines like</p> <p>19 nitrosoproline.</p> <p>20 So you need to restate the question.</p> <p>21 Q. Well, the question was any intake of</p> <p>22 NDMA or NDEA from valsartan-containing medications</p> <p>23 just a fraction of an individual's daily intake of</p> <p>24 those substances from exogenous and endogenous</p> <p>25 formation?</p>	<p style="text-align: right;">Page 197</p> <p>1 Q. We do know there's NDMA in air?</p> <p>2 A. I don't know about that. I don't</p> <p>3 think that that's a -- that's a blanket statement.</p> <p>4 It sounds much worse than it is. There's NDMA in</p> <p>5 food, there's NDMA in beer and there's NDMA in</p> <p>6 valsartan. We know that. There's no NDMA --</p> <p>7 extremely small amount -- in water.</p> <p>8 Q. Do you agree that the NDMA observed</p> <p>9 in the valsartan-containing medications is but a</p> <p>10 fraction of the NDMA to which we are exposed to</p> <p>11 exogenously and which we form endogenously?</p> <p>12 MR. SLATER: Objection.</p> <p>13 You can answer.</p> <p>14 A. No, I don't. I agree about the</p> <p>15 exogenous exposure. We already went through that,</p> <p>16 the Gushgari. But I maintain that we don't know</p> <p>17 how much NDMA and NDEAs form endogenously. It</p> <p>18 could very well be zero. So we don't know. We</p> <p>19 don't know the answer to that.</p> <p>20 Q. In the FDA workshop, was this issue</p> <p>21 of relative level of exposure from nitrosamines in</p> <p>22 valsartan-containing medications compared to our</p> <p>23 exposures exogenously and endogenously something</p> <p>24 that was discussed?</p> <p>25 A. Yes, there was quite a bit of</p>

<p style="text-align: right;">Page 198</p> <p>1 discussion about endogenous nitrosamine formation.</p> <p>2 Q. And isn't it true in the FDA workshop</p> <p>3 the conclusion that was reached among this panel</p> <p>4 of experts was that the levels of nitrosamines as</p> <p>5 impurities in drugs are likely minuscule in</p> <p>6 comparison to exogenous exposure from foods and</p> <p>7 even more so to endogenous levels?</p> <p>8 MR. SLATER: Objection.</p> <p>9 A. Nitrosamines includes -- first of</p> <p>10 all, I don't think they use the word "minuscule."</p> <p>11 I'm not sure about that. I'd have to check the</p> <p>12 transcript.</p> <p>13 Again, you're mixing apples and</p> <p>14 oranges because, as I said several times already,</p> <p>15 I think, just about everything we know about</p> <p>16 endogenous formation involves noncarcinogenic</p> <p>17 nitrosamines such as nitrosopropine. We don't</p> <p>18 have good data on the endogenous formation of the</p> <p>19 compounds found in valsartan, dimethylnitrosamine.</p> <p>20 MR. TRISCHLER: What's your next</p> <p>21 numbered exhibit?</p> <p>22 THE VIDEOGRAPHER: Our next exhibit</p> <p>23 number will be 13 and Counsel, just to let</p> <p>24 you know, I have about five minutes left on</p> <p>25 the media.</p>	<p style="text-align: right;">Page 200</p> <p>1 A. Yes.</p> <p>2 Q. Do you agree with its content?</p> <p>3 A. Yes.</p> <p>4 MR. SLATER: Objection.</p> <p>5 You can answer.</p> <p>6 Q. Please go to page 14, last paragraph</p> <p>7 of the page.</p> <p>8 About halfway through the page, it is</p> <p>9 written "The levels of nitrosamines as impurities</p> <p>10 in drug are likely minuscule in comparison to</p> <p>11 exogenous exposures from foods and even more so to</p> <p>12 endogenous levels."</p> <p>13 Did I read that correctly?</p> <p>14 A. Yes, you did. But, you know, it's a</p> <p>15 poorly written sentence, but yeah, you read it</p> <p>16 correctly. You're right, it's in the report.</p> <p>17 You're right. I read the report. I wouldn't have</p> <p>18 written it this way.</p> <p>19 Q. It's a poorly written statement that</p> <p>20 you told me you agreed with, right?</p> <p>21 A. Well, first of all, minuscule, I mean</p> <p>22 you said a few minutes ago, I think, from foods it</p> <p>23 was up to 7%. I think you said that. I don't</p> <p>24 know whether that's minuscule. And then even more</p> <p>25 so to endogenous levels.</p>
<p style="text-align: right;">Page 199</p> <p>1 MR. TRISCHLER: Please mark as</p> <p>2 Exhibit 14 --</p> <p>3 THE VIDEOGRAPHER: Thirteen.</p> <p>4 MR. TRISCHLER: Thirteen.</p> <p>5 -- the document entitled</p> <p>6 "Nitrosamines as Impurities in Drugs, Health</p> <p>7 Risk Assessment and Mitigation Public</p> <p>8 Workshop," please.</p> <p>9 THE VIDEOGRAPHER: Sure thing.</p> <p>10 (Whereupon, Exhibit 13 was marked for</p> <p>11 identification.)</p> <p>12 MR. SLATER: You're putting up part</p> <p>13 of the transcript here, Clem?</p> <p>14 MR. TRISCHLER: I'm putting up a</p> <p>15 publication from the FDA titled "Nitrosamines</p> <p>16 as Impurities in Drugs, Health Risk</p> <p>17 Assessment and Mitigation Public Workshop."</p> <p>18 Q. Do you see the first page of the</p> <p>19 Exhibit 13, sir?</p> <p>20 A. Yes.</p> <p>21 Q. This was a document that the FDA has</p> <p>22 published from the March 29 and March 30 public</p> <p>23 workshop that you participated in?</p> <p>24 A. Yes.</p> <p>25 Q. Have you read this document before?</p>	<p style="text-align: right;">Page 201</p> <p>1 Again, this is really misleading</p> <p>2 because we don't know about the -- the</p> <p>3 nitrosamine -- the endogenous data comes almost</p> <p>4 exclusively from a noncarcinogenic nitrosopropine</p> <p>5 and related nitrosothyopropine and these compounds</p> <p>6 that's that are excreted unchanged and they're</p> <p>7 noncarcinogenic.</p> <p>8 So, I mean, this sentence actually is</p> <p>9 a little misleading. I know it was written by the</p> <p>10 great FDA, but ...</p> <p>11 Q. You were --</p> <p>12 A. I was part of it. Yeah, I reviewed</p> <p>13 it. That's right. You know.</p> <p>14 Q. You were part of the great FDA panel</p> <p>15 when this was --</p> <p>16 A. I was, yeah. I was. Absolutely.</p> <p>17 Q. You have to let me ask a question.</p> <p>18 A. Okay.</p> <p>19 Q. When this was written, did you</p> <p>20 express disagreement with it?</p> <p>21 A. No, I did not.</p> <p>22 Q. Did you tell anyone at FDA that this</p> <p>23 statement was incorrect?</p> <p>24 A. No, I did not.</p> <p>25 Q. So even if we assume for the sake of</p>

<p style="text-align: right;">Page 202</p> <p>1 argument that nitrosamines like NDMA and NDEA can</p> <p>2 cause cancer in humans, what we know is that those</p> <p>3 nitrosamines can be formed both endogenously and</p> <p>4 exogenously, correct?</p> <p>5 MR. SLATER: Objection.</p> <p>6 You can answer.</p> <p>7 A. I don't think there's good evidence</p> <p>8 for endogenous formation of NDMA and NDEA.</p> <p>9 Q. I thought you told me before you were</p> <p>10 not going to express the opinion that endogenous</p> <p>11 formation does not occur.</p> <p>12 MR. SLATER: Objection.</p> <p>13 Argumentative.</p> <p>14 A. Double negative.</p> <p>15 MR. SLATER: Is there a question?</p> <p>16 A. Double negative again. I don't know.</p> <p>17 Can you rephrase your question?</p> <p>18 Q. Does endogenous formation of NDEA</p> <p>19 occur?</p> <p>20 A. I don't know.</p> <p>21 Q. Does endogenous formation of NDMA</p> <p>22 occur?</p> <p>23 A. I don't know.</p> <p>24 Q. You can't rule out the possibility</p> <p>25 that endogenous formation of NDEA and NDMA occur?</p>	<p style="text-align: right;">Page 204</p> <p>1 depositions of any of the individual plaintiffs?</p> <p>2 A. No.</p> <p>3 Q. Is there any scientific means to</p> <p>4 measure the quantity of NDEA in the human body?</p> <p>5 A. No. Not accurately.</p> <p>6 Q. I think I asked you about NDEA. For</p> <p>7 completeness, let me ask you about NDMA.</p> <p>8 Is there any scientific means to</p> <p>9 measure the quantity of NDMA in the human body?</p> <p>10 A. Not in my opinion. Not right now,</p> <p>11 no.</p> <p>12 Q. So I take it then that no such</p> <p>13 attempts have been made by you with respect to any</p> <p>14 plaintiff in this case?</p> <p>15 A. No.</p> <p>16 Q. So there's no way to do a blood test,</p> <p>17 a tissue sample or anything like that of an</p> <p>18 individual, look at it and say how much NDMA he or</p> <p>19 she might have in their body at any point in time?</p> <p>20 A. I wouldn't say that. There are ways,</p> <p>21 but I haven't done it. As far as I know, it has</p> <p>22 not been done.</p> <p>23 Q. Maybe I'm confusing myself.</p> <p>24 I thought I had asked you if there</p> <p>25 was any scientific way to measure or quantify NDMA</p>
<p style="text-align: right;">Page 203</p> <p>1 A. That is correct.</p> <p>2 Q. In your work in this case -- strike</p> <p>3 that.</p> <p>4 When we talk about exogenous intake</p> <p>5 of NDEA and NDMA, we know that can come from</p> <p>6 multiple sources, correct?</p> <p>7 A. Yes.</p> <p>8 Q. In your work in this case, have you</p> <p>9 interviewed any of the individual plaintiffs?</p> <p>10 A. No.</p> <p>11 Q. Have you reviewed any medical records</p> <p>12 from any of the individual plaintiffs?</p> <p>13 A. No.</p> <p>14 Q. Have you reviewed any questionnaires</p> <p>15 completed by any of the individual plaintiffs?</p> <p>16 A. No.</p> <p>17 Q. Have you prepared questionnaires to</p> <p>18 be submitted to any of the individual plaintiffs?</p> <p>19 A. No.</p> <p>20 Q. Have you obtained any information</p> <p>21 from any of the individual plaintiffs regarding</p> <p>22 their dietary habits, smoking history, medical</p> <p>23 history, anything like that?</p> <p>24 A. No.</p> <p>25 Q. Have you reviewed any of the</p>	<p style="text-align: right;">Page 205</p> <p>1 or NDEA in the body.</p> <p>2 A. There's no established method that's</p> <p>3 accepted as far as I know, but that doesn't mean</p> <p>4 it can't be done.</p> <p>5 Q. How would you hypothetically do it if</p> <p>6 there's no established method for doing it?</p> <p>7 A. I would use mass spectrometry and I</p> <p>8 would use an internal standard that labeled</p> <p>9 internal standard of dimethylamine that would tell</p> <p>10 me whether any artifact formation or any other</p> <p>11 interference was occurring in the method. It can</p> <p>12 be done, but it hasn't been done as far as I know.</p> <p>13 Q. So without some baseline, you don't</p> <p>14 have any data to establish sort of a baseline</p> <p>15 nitrosamine level for any particular plaintiff</p> <p>16 based on their exogenous and endogenous exposures</p> <p>17 to these particular nitrosamines, right?</p> <p>18 A. No. You know, only -- well, what we</p> <p>19 already discussed, I mean, from levels in food and</p> <p>20 that kind of thing. No, not actual measurements.</p> <p>21 Q. So without a baseline --</p> <p>22 A. Like a before and after they took the</p> <p>23 pill or something like that, we don't have that.</p> <p>24 Q. Right.</p> <p>25 So without a per person, individual</p>

<p style="text-align: right;">Page 206</p> <p>1 baseline, there's no -- you don't have any basis</p> <p>2 to opine whether NDMA intake or NDEA intake from</p> <p>3 valsartan-containing medications for any plaintiff</p> <p>4 in this case represented a 1%, 2%, 5% increase in</p> <p>5 their daily exposure to these nitrosamines,</p> <p>6 correct?</p> <p>7 A. No, we don't have that data.</p> <p>8 Q. We don't have that data for either</p> <p>9 NDMA or NDEA?</p> <p>10 A. Correct.</p> <p>11 Q. Are you familiar with --</p> <p>12 A. It would be based on estimates of</p> <p>13 exposure that we know -- we know the amounts in</p> <p>14 food and beer and the things that we discuss, but</p> <p>15 actual measurements we don't have.</p> <p>16 Q. Are you familiar with the Johnson</p> <p>17 paper on permitted daily exposure limits for</p> <p>18 nitrosamines?</p> <p>19 A. Show me the paper.</p> <p>20 MR. TRISCHLER: Sure. I guess it's</p> <p>21 14 I think is what we're up to.</p> <p>22 THE VIDEOGRAPHER: Counsel, just</p> <p>23 we're about seven minutes over.</p> <p>24 Do you mind if we change the media?</p> <p>25 MR. SLATER: Why don't we break for</p>	<p style="text-align: right;">Page 208</p> <p>1 highlight, Bill, the top portion.</p> <p>2 Q. You'll note that the article was</p> <p>3 received in March of this year and accepted for</p> <p>4 publication in May.</p> <p>5 I'm just wondering if you had a</p> <p>6 chance to review this paper or you recall</p> <p>7 reviewing this paper before you wrote your report</p> <p>8 in July of this year?</p> <p>9 A. I haven't seen this.</p> <p>10 Q. In this report, Johnson and his</p> <p>11 colleagues calculate a permitted daily exposure</p> <p>12 level for NDMA and NDEA.</p> <p>13 Have you ever calculated a permitted</p> <p>14 daily exposure limit for any compound?</p> <p>15 A. No.</p> <p>16 Q. Are you familiar with the concept of</p> <p>17 a permitted daily exposure limit?</p> <p>18 MR. SLATER: Objection.</p> <p>19 You can answer.</p> <p>20 A. Yes, in general. But I'm not sure</p> <p>21 about the language.</p> <p>22 Q. Well, it's my understanding that in</p> <p>23 the field of toxicology, a permitted daily</p> <p>24 exposure limit generally refers to a dose that is</p> <p>25 unlikely to cause an adverse effect in an</p>
<p style="text-align: right;">Page 207</p> <p>1 lunch now? We're way past --</p> <p>2 MR. TRISCHLER: Oh, okay. Sorry</p> <p>3 about that. I lost -- for some reason, my</p> <p>4 clock on my computer is off.</p> <p>5 THE VIDEOGRAPHER: The time is</p> <p>6 2:04 p.m.</p> <p>7 This ends media three.</p> <p>8 (Recess taken)</p> <p>9 THE VIDEOGRAPHER: The time is now</p> <p>10 2:57.</p> <p>11 This begins media four.</p> <p>12 You may proceed.</p> <p>13 (Whereupon, Exhibit 14 was marked for</p> <p>14 identification.)</p> <p>15 Q. Dr. Hecht, are you familiar -- I'm</p> <p>16 not sure if I asked you this question before the</p> <p>17 break. I thought I was ready to introduce a paper</p> <p>18 by Mr. Johnson entitled "Permitted Daily Exposure</p> <p>19 Limits for Noteworthy Nitrosamines." I think that</p> <p>20 would be Exhibit 14.</p> <p>21 Have you seen this paper before?</p> <p>22 Let me know if you need it</p> <p>23 highlighted or blown up.</p> <p>24 A. I don't recognize it.</p> <p>25 MR. TRISCHLER: If you could, just</p>	<p style="text-align: right;">Page 209</p> <p>1 individual is exposed at or below this dose every</p> <p>2 day of a lifetime.</p> <p>3 Okay?</p> <p>4 So accepting that definition, are</p> <p>5 you -- have you ever attempted to calculate a PDE</p> <p>6 for any nitrosamine?</p> <p>7 A. No.</p> <p>8 Q. If you look at -- I think it's the</p> <p>9 page 302 of this paper. There's a chart or a</p> <p>10 table at the top and you'll see that in the last</p> <p>11 row or last column, Johnson and his colleagues</p> <p>12 calculated a PDE for NDMA of 6.2 micrograms and a</p> <p>13 PDE for NDEA of 2.2 micrograms.</p> <p>14 Do you see that?</p> <p>15 A. Mm-hmm. Yeah.</p> <p>16 Q. We talked about the conversions</p> <p>17 before, but that equates to roughly</p> <p>18 6,200 nanograms and 2,200 nanograms, right?</p> <p>19 A. Right.</p> <p>20 Q. And if you go back to the test data</p> <p>21 from Mylan that you mentioned in your report, that</p> <p>22 test data shows an NDEA range for API batches of</p> <p>23 0.1 parts per million to 1.57 parts per million</p> <p>24 and I represented to you that the mean</p> <p>25 concentration was calculated at 0.47.</p>

<p style="text-align: right;">Page 210</p> <p>1 Do you recall that?</p> <p>2 A. What was the range again?</p> <p>3 Q. 0.1 parts per million to 1.57 parts</p> <p>4 per million. That's what you wrote in your</p> <p>5 report.</p> <p>6 A. Okay.</p> <p>7 Q. And I had represented to you that</p> <p>8 that range resulted in a mean of 0.47.</p> <p>9 MR. SLATER: Did you say NDMA or NDEA</p> <p>10 for that range you just gave?</p> <p>11 MR. TRISCHLER: NDEA, sir.</p> <p>12 MR. SLATER: Gotcha.</p> <p>13 A. Okay.</p> <p>14 Q. Converting that parts per million to</p> <p>15 a nanogram level based on the 320 milligram dose</p> <p>16 results in a nanogram concentration of about</p> <p>17 150 nanograms.</p> <p>18 Do you recall that math that we did</p> <p>19 before?</p> <p>20 A. Yes.</p> <p>21 Q. So if we use that calculation of</p> <p>22 150 nanograms of NDEA in a tablet of Mylan's</p> <p>23 valsartan-containing medication, it's well under</p> <p>24 the PDE established by Johnson in his</p> <p>25 peer-reviewed study, correct?</p>	<p style="text-align: right;">Page 212</p> <p>1 Do you generally recall that</p> <p>2 discussion?</p> <p>3 A. Mm-hmm. Yes.</p> <p>4 Q. And you -- we talked about some of</p> <p>5 the literature that you reviewed earlier,</p> <p>6 specifically some of the animal studies, correct?</p> <p>7 A. Yes.</p> <p>8 Q. In addition to the animal studies, I</p> <p>9 note in your report, though, that you also discuss</p> <p>10 a number of dietary studies. I think those are</p> <p>11 primarily cited at pages 14 and 15 of your report.</p> <p>12 Is that right?</p> <p>13 A. Yes.</p> <p>14 Q. Similar to what we talked about</p> <p>15 before, was there a particular method that you</p> <p>16 used to decide what dietary studies you were going</p> <p>17 to include in this report?</p> <p>18 A. Well, I looked into literature on</p> <p>19 epidemiology studies that take into account</p> <p>20 nitrosamine exposure.</p> <p>21 Q. Would we be able to go back at this</p> <p>22 point in time and recreate what literature you</p> <p>23 would have looked at by means of a -- the results</p> <p>24 of a literature search or notes or anything that</p> <p>25 you maintain to tell us what kind of search you</p>
<p style="text-align: right;">Page 211</p> <p>1 A. Yes.</p> <p>2 Q. In fact, the mean nanogram</p> <p>3 concentration would be about 5% of that daily PDE.</p> <p>4 Correct?</p> <p>5 A. Right. Yes.</p> <p>6 Q. Do you have any evidence to suggest</p> <p>7 to this jury that a plaintiff in this litigation</p> <p>8 who consumed valsartan-containing medication that</p> <p>9 came from Mylan ever received a pill that</p> <p>10 contained nitrosamines above the PDE established</p> <p>11 by Johnson and his colleagues?</p> <p>12 A. No, I don't.</p> <p>13 Q. Earlier in the deposition --</p> <p>14 A. No, it's still maintained that none</p> <p>15 of that should be there. It should be zero.</p> <p>16 Q. Earlier in the deposition, I had</p> <p>17 asked you a few questions about how you went about</p> <p>18 doing your work in this case and you told me that</p> <p>19 there were, you know, three components of it:</p> <p>20 One, reviewing publically-available information</p> <p>21 about the valsartan medications; two, looking at</p> <p>22 the scientific literature; and three, reviewing</p> <p>23 documents that came to you from plaintiffs'</p> <p>24 counsel that related to documents from the</p> <p>25 manufacturer's defendants.</p>	<p style="text-align: right;">Page 213</p> <p>1 did for the literature?</p> <p>2 A. I didn't keep records of the -- of my</p> <p>3 literature search.</p> <p>4 Q. I assume that you would agree with me</p> <p>5 that following a scientific approach to causation</p> <p>6 requires a review of all the relevant literature?</p> <p>7 A. Yes.</p> <p>8 Q. Were there any dietary intake studies</p> <p>9 that you -- addressing the potential</p> <p>10 carcinogenicity of NDMA or NDEA in foods that you</p> <p>11 reviewed beyond the ones that you listed in your</p> <p>12 report?</p> <p>13 A. No, I don't believe so. I think</p> <p>14 they're all listed in the report. It's possible</p> <p>15 that, you know, I may have missed something, but I</p> <p>16 think they're all in the report.</p> <p>17 Q. My apologies. I thought you had</p> <p>18 finished.</p> <p>19 Would you agree with me that there</p> <p>20 have been many observational studies reported in</p> <p>21 the literature where scientists observe no</p> <p>22 statistically significant association between</p> <p>23 nitrosamine intake and food and the cause of</p> <p>24 various cancers?</p> <p>25 A. No. Repeat the question.</p>

<p style="text-align: right;">Page 214</p> <p>1 Q. Sure.</p> <p>2 A. What did you say?</p> <p>3 Q. I said have there been observational</p> <p>4 studies reported in the literature where</p> <p>5 scientists observed no statistically significant</p> <p>6 association between nitrosamine intake and food</p> <p>7 and the cause of various cancers?</p> <p>8 A. What do you mean by observational?</p> <p>9 Q. Well, all of these dietary intake</p> <p>10 studies are observational.</p> <p>11 A. Well, sure, broadly speaking, but I'm</p> <p>12 not sure what you mean by observational.</p> <p>13 Q. Let me see if I could ask another</p> <p>14 question.</p> <p>15 A. It's a very broad term.</p> <p>16 Q. I was trying to --</p> <p>17 A. I'm not sure what that means.</p> <p>18 Q. I was just trying to be sort of all</p> <p>19 encompassing with the question. Let me ask it a</p> <p>20 different way then.</p> <p>21 There have been studies that have</p> <p>22 been reported in the literature where scientists</p> <p>23 attempted to evaluate NDMA and NDEA content in</p> <p>24 food and they reported no statistically</p> <p>25 significant association between that intake and</p>	<p style="text-align: right;">Page 216</p> <p>1 looking at pages 14 and 15 of your report -- what</p> <p>2 it appears to me that you did was to discuss the</p> <p>3 studies that you believe reported some association</p> <p>4 between dietary intake of nitrosamines and some</p> <p>5 cancers while ignoring any studies that reached a</p> <p>6 contrary result.</p> <p>7 Is that accurate?</p> <p>8 A. I focused on the ones that showed a</p> <p>9 relationship, yes.</p> <p>10 Q. And you did not discuss the ones that</p> <p>11 don't?</p> <p>12 MR. SLATER: Objection.</p> <p>13 Lack of foundation.</p> <p>14 You can answer.</p> <p>15 A. I don't know. I mean, I may not have</p> <p>16 discussed every study in the literature.</p> <p>17 Q. But what you did do -- and it's on</p> <p>18 page 15, if you want to take a look -- was you</p> <p>19 sort of covered the omission of non-favorable</p> <p>20 studies with one paragraph in which you said</p> <p>21 "Studies do not find a significant association or</p> <p>22 raise questions. This can be explained by smaller</p> <p>23 relatively small sample size, inadequate follow-up</p> <p>24 period to capture all cancers, bias/inadequate</p> <p>25 dose quantification, potentially mitigating</p>
<p style="text-align: right;">Page 215</p> <p>1 cancer.</p> <p>2 Agreed?</p> <p>3 A. Sure. But, I mean, there are also</p> <p>4 other studies that do report an association, so I</p> <p>5 think your question should be rephrased.</p> <p>6 Q. That was sort of my point, is that</p> <p>7 there are studies that go both ways. There are</p> <p>8 studies that have been published that report a</p> <p>9 statistically significant association between NDMA</p> <p>10 intake and some foods and the development of</p> <p>11 cancer and there are other studies that have</p> <p>12 reached a contrary result. That's the question I</p> <p>13 was asking.</p> <p>14 A. Mm-hmm. There are both types of</p> <p>15 results -- that's true -- out there.</p> <p>16 Q. In your report --</p> <p>17 A. It's a very challenging study to do.</p> <p>18 Q. Sure.</p> <p>19 In your report, did you attempt to</p> <p>20 list or collect or identify all of those studies</p> <p>21 where no association was found between NDMA in</p> <p>22 food and the onset or development of cancer?</p> <p>23 A. No, I did not.</p> <p>24 Q. What it appears to me that you did --</p> <p>25 and please correct me if I'm wrong -- again, I'm</p>	<p style="text-align: right;">Page 217</p> <p>1 dietary factors such as vitamin C intake and</p> <p>2 others."</p> <p>3 Right?</p> <p>4 A. Right.</p> <p>5 Q. So what it sounds to me like what</p> <p>6 you're suggesting is that you're acknowledging</p> <p>7 that the dietary intake studies evaluating the</p> <p>8 role of nitrosamines in diet and the onset of</p> <p>9 cancer have gone both ways, right?</p> <p>10 A. Yes.</p> <p>11 Q. And what it sounds like what you did</p> <p>12 in your report is simply to say that in the</p> <p>13 studies that find no association, you discredit</p> <p>14 those by saying that they're subject to either</p> <p>15 poor study design or confounding factors?</p> <p>16 MR. SLATER: Objection.</p> <p>17 You can answer.</p> <p>18 A. Well, you know, just about all of</p> <p>19 these studies can be criticized for one reason for</p> <p>20 another. I mean, these types of studies are</p> <p>21 extremely difficult to do, so they can be</p> <p>22 criticized, but yeah, I didn't cover all of the --</p> <p>23 I didn't attempt to cover all of the studies of</p> <p>24 diet and nitrosamine content in foods and cancer.</p> <p>25 I did not attempt to do that.</p>

<p style="text-align: right;">Page 218</p> <p>1 Q. And I understand --</p> <p>2 A. But I did give examples of where</p> <p>3 nitrosamine contamination in food has been linked</p> <p>4 to cancer and there are a number of them.</p> <p>5 Q. Right. I understand that there are</p> <p>6 difficulties in doing these studies and that they</p> <p>7 all have their limits, but when I read your</p> <p>8 report, what it suggests is that the only studies</p> <p>9 that you criticized as being limited by</p> <p>10 confounding factors are the ones that found no</p> <p>11 association between cancer and NDMA intake?</p> <p>12 A. That's not necessarily true.</p> <p>13 Q. Isn't that what that paragraph in</p> <p>14 page 15 means when we read it?</p> <p>15 A. I don't know. You know, I mean, this</p> <p>16 criticism can also apply to some of the positive</p> <p>17 sides. It's a general criticism.</p> <p>18 Q. Well, let's take a look at some of</p> <p>19 the studies that you do cite to, if we can.</p> <p>20 Okay?</p> <p>21 A. Okay.</p> <p>22 MR. TRISCHLER: You cite to a study</p> <p>23 by Goodman, G-O-O-D-M-A-N, entitled "High Fat</p> <p>24 Foods and the Risk of Lung Cancer."</p> <p>25 Can we mark that as Exhibit 15?</p>	<p style="text-align: right;">Page 220</p> <p>1 smokers with a high intake of foods rich in fat</p> <p>2 and animal protein and who have a preference for</p> <p>3 cured meats are at increased risk of lung cancer.</p> <p>4 A. That's what they concluded.</p> <p>5 Q. That's not really a surprising or</p> <p>6 controversial finding, is it?</p> <p>7 A. No. A study like this would be very</p> <p>8 difficult to do in smokers. I could be critical</p> <p>9 of this study for that reason, but this is what</p> <p>10 they found and it's a good group. It's a very</p> <p>11 highly respected group.</p> <p>12 Q. When we talk about confounding, any</p> <p>13 attempt to link these results to NDMA consumption</p> <p>14 would be limited by confounding factors relating</p> <p>15 to dietary intake of other fatty foods such as</p> <p>16 dairy products and desserts, right? That would be</p> <p>17 one confounding factor?</p> <p>18 A. The main confounding factor would be</p> <p>19 smoking. That would blow away other confounding</p> <p>20 factors. But they found a risk in addition to</p> <p>21 smoking from cured meats and foods rich in fat and</p> <p>22 animal protein. It's a very difficult study to</p> <p>23 do. Very challenging because of the overwhelming</p> <p>24 effect of smoking.</p> <p>25 Q. While smoking might be the primary</p>
<p style="text-align: right;">Page 219</p> <p>1 (Whereupon, Exhibit 15 was marked for</p> <p>2 identification.)</p> <p>3 Q. Are you familiar with this work, sir?</p> <p>4 A. Yes, I am.</p> <p>5 Q. What the authors of this study found</p> <p>6 was that there was an association between lung</p> <p>7 cancer and a diet that was rich in fats, correct?</p> <p>8 A. Yes.</p> <p>9 Q. They never excluded and they could</p> <p>10 not exclude was any association was due to dairy</p> <p>11 products, desserts or other fatty foods, correct?</p> <p>12 A. I don't know about dairy products.</p> <p>13 I'd have to look at it more closely.</p> <p>14 Q. You could look at the --</p> <p>15 A. I'd have to read it.</p> <p>16 Q. I can have our technician --</p> <p>17 A. I mean do they -- I think they</p> <p>18 describe the questionnaire in there, so I have to</p> <p>19 look at that more carefully.</p> <p>20 MR. TRISCHLER: Bill, can you</p> <p>21 highlight the top portion, please?</p> <p>22 THE WITNESS: Yes.</p> <p>23 Q. So what the paper says in that last</p> <p>24 sentence that was highlighted there is that what</p> <p>25 the data from the Goodman study indicates is that</p>	<p style="text-align: right;">Page 221</p> <p>1 confounding factor, there are others, correct?</p> <p>2 A. Yes.</p> <p>3 Q. By the way, the control group in this</p> <p>4 Goodman study was, I think, 326 subjects.</p> <p>5 Was that a significant and adequate</p> <p>6 test sample size in your judgment?</p> <p>7 A. That's relatively small by current</p> <p>8 standards. This was published in 1992, I believe.</p> <p>9 That's a relatively small sample size.</p> <p>10 Q. Sorry.</p> <p>11 Do you agree that a good scientist</p> <p>12 would not draw conclusions or inferences from a</p> <p>13 study that even the authors of that study would</p> <p>14 not support?</p> <p>15 MR. SLATER: Objection.</p> <p>16 We went through this earlier.</p> <p>17 A. I'm not sure what that question even</p> <p>18 means. Why wouldn't the authors support their own</p> <p>19 study? I don't understand that.</p> <p>20 Q. I said they would not support.</p> <p>21 Can you as a scientist reach</p> <p>22 conclusions that the authors themselves do not</p> <p>23 draw?</p> <p>24 MR. SLATER: Objection.</p> <p>25 You went over this earlier, Counsel.</p>

<p style="text-align: right;">Page 222</p> <p>1 I thought we're not going to</p> <p>2 duplicate areas of questioning in light of</p> <p>3 the time issue.</p> <p>4 A. For this study or any study?</p> <p>5 Q. For any study.</p> <p>6 MR. SLATER: I object.</p> <p>7 Counsel, you do realize you went over</p> <p>8 this entire line of questioning earlier in</p> <p>9 the deposition, right? You're just going to</p> <p>10 ignore me, I guess? Okay. Well, I don't</p> <p>11 appreciate that you're going to go through a</p> <p>12 line of questioning you already did hours ago</p> <p>13 or are you representing you didn't ask this</p> <p>14 question already and go down this line</p> <p>15 already?</p> <p>16 MR. TRISCHLER: I've got a question</p> <p>17 pending. I'm just waiting on an answer,</p> <p>18 Adam.</p> <p>19 MR. SLATER: You're ignoring me?</p> <p>20 Thank you.</p> <p>21 A. What was the question again?</p> <p>22 Q. Is it good practice for a scientist</p> <p>23 to draw conclusions from a paper that the authors</p> <p>24 of that paper do not support?</p> <p>25 MR. SLATER: Again, I object to this</p>	<p style="text-align: right;">Page 224</p> <p>1 Q. You also cite to a paper that was</p> <p>2 written by a gentleman named Paul Knekt,</p> <p>3 K-N-E-K-T. I'm sure I'm mispronouncing that.</p> <p>4 But are you familiar with the paper?</p> <p>5 A. Yes.</p> <p>6 MR. TRISCHLER: We'll mark that as</p> <p>7 Exhibit 16, I think.</p> <p>8 (Whereupon, Exhibit 16 was marked for</p> <p>9 identification.)</p> <p>10 Q. You cited to the Knekt paper in your</p> <p>11 report in this case, correct?</p> <p>12 A. Yes.</p> <p>13 Q. Do you recall reading this study</p> <p>14 and --</p> <p>15 A. Yes, I read it. Absolutely. I did</p> <p>16 absolutely read it.</p> <p>17 Q. One of the first things that I note</p> <p>18 right off the bat when I read this study is in the</p> <p>19 very first sentence at the top, the authors note</p> <p>20 that the relationship of dietary nitrosamines to</p> <p>21 human cancer is uncertain.</p> <p>22 Do you see that?</p> <p>23 A. Yes.</p> <p>24 Q. We talked about how some studies are</p> <p>25 difficult, some are flawed, some are well</p>
<p style="text-align: right;">Page 223</p> <p>1 and I'll refer Counsel to the Eighth Circuit</p> <p>2 decision that came out yesterday that</p> <p>3 addressed this exact question and he knows</p> <p>4 it, I'm sure, and asked these questions</p> <p>5 earlier in the deposition. I don't</p> <p>6 appreciate that.</p> <p>7 We'll take it into account if and</p> <p>8 when defense counsel asks for more than seven</p> <p>9 hours on the record with this witness.</p> <p>10 You can answer.</p> <p>11 A. There may be different</p> <p>12 interpretations of data. It for sure can happen.</p> <p>13 Q. Do you agree that --</p> <p>14 A. The authors of a paper may interpret</p> <p>15 their data in a certain way and, you know, then</p> <p>16 it's reviewed and the reviewers may agree with it,</p> <p>17 the editors of the journal may agree with it, but</p> <p>18 other scientists may not agree with the</p> <p>19 interpretation.</p> <p>20 Q. Do you agree that a scientist should</p> <p>21 not cherry-pick data from a study that might</p> <p>22 support his or her hypothesis while ignoring other</p> <p>23 parts of the study that call the conclusion into</p> <p>24 question?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">Page 225</p> <p>1 designed, some are not.</p> <p>2 Was this Knekt study one that you</p> <p>3 considered to be a good, well-designed study?</p> <p>4 A. Show me the -- show me the -- you</p> <p>5 have to show me more.</p> <p>6 Q. Which part --</p> <p>7 A. I want to make sure -- hold on a</p> <p>8 second.</p> <p>9 Q. Sure.</p> <p>10 A. Let me just look at my own notes.</p> <p>11 Yes. Okay. Yes, go ahead. What was your</p> <p>12 question.</p> <p>13 Q. I think I asked you whether in your</p> <p>14 judgment this was a good, well-designed study.</p> <p>15 A. Yes, it was.</p> <p>16 Q. Can we rely on its conclusions then?</p> <p>17 A. Yes.</p> <p>18 MR. SLATER: Objection.</p> <p>19 Q. In this study by Knekt, the authors</p> <p>20 observed that there was no increased risk of</p> <p>21 cancer from NDMA for any cancers of the GI tract.</p> <p>22 Correct?</p> <p>23 A. They found an increased risk of</p> <p>24 colorectal cancer among individuals with a high</p> <p>25 intake of NDMA. That's what it says.</p>

<p style="text-align: right;">Page 226</p> <p>1 Q. Right. I didn't ask you about that, 2 though. My question was -- 3 A. What did you ask me then? 4 Q. My question was -- 5 A. The GI tract -- 6 Q. -- the authors observed there was no 7 increased risk of NDMA for any cancers of the GI 8 tract. 9 Is that true or not? 10 A. You know -- 11 Q. I guess I should say any other 12 cancers of the GI tract. 13 A. Yes, that's true. They observed for 14 colorectal. Colorectal. 15 Q. They observed no increase -- 16 A. In the first sentence of the 17 discussion -- 18 Q. They did -- 19 A. -- "We found an increased risk of 20 colorectal cancer among individuals with a high 21 intake of NDMA and of colorectal" -- it's part of 22 the GI tract, I think. 23 Q. Thank you. 24 They observed no increased risk of 25 stomach cancer, correct?</p>	<p style="text-align: right;">Page 228</p> <p>1 food in order to make the calculations. So it's 2 not like somebody self-reports, you know, I don't 3 think I was exposed to much dimethylnitrosamine 4 yesterday or anything like that. It's the 5 self-reporting for the kinds of foods that they -- 6 which is pretty reliable. 7 So they ask the subjects -- you know, 8 they could give them a big table of different 9 types of food and methods of preparation, 10 everything, and the subjects fill out these 11 questionnaires so that the investigators know 12 basically what the person's diet consisted of. 13 Then they use that information and 14 tables which are developed by the government 15 agencies in that country -- for example, in 16 Europe, by the EU -- tables that give the 17 nitrosamine content of many different types of 18 food in great accuracy and they combine this 19 information with the personal dietary information. 20 It's not like they're asking people "Did you 21 consume any nitrosamines today?" The people 22 answering the questions have no idea. They're 23 just -- they're just explaining what their 24 customary diet is, which people can do with great 25 accuracy. This is particularly true in cohort</p>
<p style="text-align: right;">Page 227</p> <p>1 A. Correct. 2 Q. They observed no increased risk of 3 esophageal cancer, correct? 4 A. Correct. 5 Q. While as you point out in this Knekt 6 study the authors did find an association between 7 NDMA and colorectal cancer, even those authors 8 observed that this observation might be due to 9 confounding, correct? 10 A. It's possible. 11 Q. It's not possible. It's what they 12 said. 13 A. Yes, I'm agreeing with you. It's 14 possible that it could be due to confounding. 15 That's always an issue in epidemiology studies. 16 Q. When we talk about dietary studies 17 like this and others that you cited and reviewed, 18 they're all based on self-reported dietary 19 behavior, correct? 20 A. No. Yes. Yes, they are. Yes and 21 no. Okay? So I mean in some of these studies -- 22 so they, you know, the subjects fill out 23 questionnaires about diet. That's self-reporting. 24 But the investigators used data -- very extensive 25 data -- on dimethyl and dimethylnitrosamine in</p>	<p style="text-align: right;">Page 229</p> <p>1 studies where you're interviewing healthy people 2 and then following them for years. 3 Q. Have you finished your answer? 4 A. Yes. 5 Q. Have you seen any of the 6 questionnaires that were used in the Knekt study 7 that were talked about right now? 8 A. No, I didn't see the actual 9 questionnaires. 10 Q. Have you seen any of the -- 11 A. I did not. 12 Q. Have you seen any of the 13 questionnaires in any of the studies that you cite 14 in your paper? 15 A. No, I haven't seen the actual 16 questionnaires, but I'm familiar with -- I'm 17 familiar with epidemiologists, I'm familiar with 18 the general topic of diet and cancer from my 19 previous experience in cancer research and from 20 having served on study sections and having been 21 involved in evaluations of areas -- lifestyle 22 habits and cancer, etc., etc. 23 So I've been in a lot of -- I've been 24 on many different committees that have evaluated 25 this kind of work. I've worked with</p>

<p style="text-align: right;">Page 230</p> <p>1 epidemiologists, so I'm familiar with diet and 2 cancer studies and the approaches that are used, 3 but I didn't see the -- I didn't see the 4 particular diet questionnaire that was used for 5 this study or for any of the other studies for 6 that matter. 7 MR. TRISCHLER: Object and move to 8 strike as non-responsive. 9 Q. Did you see any of the tables that 10 were used to estimate NDMA exposures in the Knekt 11 study? 12 A. I didn't see the tables themselves, 13 but I'm familiar with this kind of table. 14 Q. I didn't ask if you were familiar -- 15 A. All right. 16 Q. I said did you -- 17 A. You asked me the question. Okay? 18 Q. Right -- 19 A. So I'm telling you I'm familiar with 20 the studies that are done, the kind of tables. 21 All right? 22 Q. I appreciate that, but I'm entitled 23 to answers to the questions I ask. 24 Did you see the tables that were 25 used --</p>	<p style="text-align: right;">Page 232</p> <p>1 well-developed methods. 2 Q. You said you worked with FSA and are 3 working with them right now, correct? 4 A. Yes, that's right. 5 Q. Have you seen FSA publications 6 estimating NDMA content in various foods? 7 A. We're working on it. 8 Q. You're working on it? Have you 9 seen -- 10 A. I've seen the data. Yes, I've seen 11 the data. 12 Q. Have they ever published any of it? 13 A. Not yet, no. 14 Q. Okay. 15 So if FSA hasn't published any of its 16 data, none of the authors of any of these papers 17 would have ever used it, correct? 18 A. No, no, no. They published data 19 before. I'm talking about this particular report. 20 There's plenty of published data on nitrosamine 21 levels in food and plenty of unpublished data also 22 by government regulatory authorities. 23 Q. I'm asking you about FSA because you 24 brought them up. 25 A. Yeah. I'm telling you what they're</p>
<p style="text-align: right;">Page 231</p> <p>1 A. No. 2 Q. Did you see the tables used in any of 3 the studies that you cite to calculate nitrosamine 4 or to estimate nitrosamine exposures? 5 A. I did not see the actual raw data 6 tables, no. I depended on the published studies. 7 The published information. 8 Q. In all of these -- 9 A. But I'm familiar with the kinds of 10 tables that they're using. I am a consultant for 11 the FSA. That's the European Food Safety 12 Authority. I'm familiar with the kinds of data 13 they have and that's the kind of data that was 14 used in these studies. 15 Q. Are you finished? 16 In any of the studies that you cite, 17 is the actual NDMA content in the foods consumed 18 by the subjects ever measured? 19 A. Not in the specific foods, but in the 20 categories of foods, yes. Definitely. 21 Q. Measured by whom? 22 A. I can't give you an answer to that 23 question, but going back to what I said before, 24 FSA and others have consulting laboratories that 25 make these measurements using well-established and</p>	<p style="text-align: right;">Page 233</p> <p>1 doing now. 2 Q. Try to let me ask the question, 3 please. 4 A. I'm not sure exactly what they were 5 doing at the time of some of these other studies, 6 but there's plenty of -- there's plenty of data 7 out there, reliable data on nitrosamine content in 8 various foods. 9 MR. TRISCHLER: Object and move to 10 strike as non-responsive. 11 Q. Sir, has FSA ever published any data 12 on nitrosamine -- on nitrosamine levels in foods? 13 A. I believe they have. 14 Q. Have you ever seen it? 15 A. Maybe. 16 Q. Do you have it? 17 A. I don't have it in my hands. I'd 18 have to look -- FSA has the so-called FSA Journal 19 where they publish a very detailed compendium and 20 it's very likely that there's something in there 21 on nitrosamines in food, but I can't cite it 22 offhand. 23 Q. One of the things that -- 24 A. You know, you can look. Look in the 25 FSA Journal.</p>

<p style="text-align: right;">Page 234</p> <p>1 Q. One of the things that you and I 2 talked about a few minutes ago was that the 3 dietary studies have been inconsistent in terms of 4 knowing an association between dietary intake of 5 nitrosamines and cancer, correct? 6 A. Yes. 7 Q. And just by way of one example, you 8 cited to a paper that was published by an author 9 named Loh, L-O-H. 10 Do you recall that paper? 11 A. Yes. 12 MR. TRISCHLER: One thing I wanted to 13 ask you about is if you -- we'll mark that as 14 Exhibit 16, I think, and 17 maybe. 15 THE VIDEOGRAPHER: We're on 17. 16 (Whereupon, Exhibit 17 was marked for 17 identification.) 18 MR. TRISCHLER: If you go to 1057 of 19 that document, please, the first paragraph of 20 text below the table, can you highlight that 21 for the benefit of the witness? 22 Q. Are you able to see what is on the 23 screen, sir? 24 A. Yes. 25 Q. I see that you referred earlier to</p>	<p style="text-align: right;">Page 236</p> <p>1 MR. SLATER: Objection. 2 That wasn't the testimony. 3 You can answer. 4 A. What's your question? 5 Q. I'm trying to understand when you 6 made reference before that you wanted to "pull 7 your notes," I'm trying to understand what you 8 meant by notes. 9 A. Yes. The binder. I read the papers 10 in the binder and as I read them, I circled or 11 underlined certain statements that I thought might 12 be relevant. 13 Q. Did you write any text -- 14 A. No. 15 Q. -- in those notes? 16 A. No, I did not. 17 Q. So if we -- what we're looking at now 18 on Exhibit 17 is a part of the Loh paper. It 19 looks like you have the actual paper in your 20 notebook, correct, or binder? 21 A. This is American Journal of Clinical 22 Nutrition. 23 Is that the one you're talking about? 24 Q. Yes, sir. 25 A. 2011?</p>
<p style="text-align: right;">Page 235</p> <p>1 some notes and you pulled out, I'm guessing, some 2 notes. It appears you're looking at something. 3 What are you looking at now? 4 A. I'm looking at the Loh paper. 5 Q. Before you mentioned that you had 6 some notes when I think I was asking you about the 7 Knekt paper we had out before. 8 Do you have notes that you took from 9 your review of these studies? 10 A. What do you mean, notes? I read the 11 papers and, you know, I underlined and circled 12 certain passages. 13 Q. Did you write any notes based on -- 14 A. No, I didn't write any notes. No. 15 Q. So what you have in front of you then 16 is just a binder of studies? 17 A. Yes. 18 Q. Are there any studies -- thank you. 19 Are there any studies in the binder 20 that are not cited in your report? 21 A. No. All of these come from my 22 report. 23 Q. And the only markings that you made 24 in your review then are highlighting and circling 25 or underlining those types of things?</p>	<p style="text-align: right;">Page 237</p> <p>1 Q. Yes. 2 A. Yes. 3 Q. What we were talking about before, 4 again, is how the studies have been inconsistent 5 and that's one of the things that Dr. Loh observes 6 in this paper, correct? 7 A. Yes. 8 Q. Basically, as we look at -- as we're 9 looking at right here, what Loh observed was that 10 there'd been published studies with respect to 11 gastric cancer that go both ways. Some report a 12 positive association with gastric cancer, while 13 others do not, right? 14 A. Insufficient evidence for esophageal 15 cancer, but a positive association between 16 nitrosamine intake and gastric cancer. So I think 17 you said -- I don't think that's what you said. 18 You said a positive association 19 between nitrite and nitrosamine intake and gastric 20 cancer. That's what Loh is saying. Not what you 21 said. Insufficient evidence for esophageal 22 cancer. I think you said -- 23 Q. I'm looking at -- 24 A. -- both positive and negative -- 25 Q. I'm looking at the sentence that says</p>

<p style="text-align: right;">Page 238</p> <p>1 in his review -- "In this review, cohort studies 2 reported no association for nitrite and NDMA 3 intakes with gastric cancer risk." 4 Do you see that? 5 A. Cohort studies. Right. Cohort 6 studies. 7 Q. Right. That's what I'm saying. 8 The studies on gastric cancer and 9 NDMA have gone both ways. Some have said there's 10 an association, others have found to the contrary. 11 A. Correct. Correct. You're right. 12 Q. Loh is simply reporting that, 13 correct? 14 A. Yes. 15 Q. In Loh's own study, it goes on to 16 note that they did not find a statistically 17 significant association between NDMA and colon 18 cancer, right? 19 A. I think they found association with 20 rectal cancer, but not colon cancer. 21 Q. Correct. 22 They found no association with 23 gastric cancer? 24 A. Correct. 25 MR. SLATER: Objection.</p>	<p style="text-align: right;">Page 240</p> <p>1 you if you would agree with me that given the 2 inconsistencies that have been observed in the 3 findings in these dietary studies that one cannot 4 rely on those studies to suggest a causal 5 connection between NDMA intake and cancer. 6 A. No, I do not agree whatsoever. 7 Q. Are you familiar with -- 8 A. There's plenty of evidence from these 9 studies. It's not totally consistent in the sense 10 that different tissues are implicated in different 11 studies, but there's -- overall there are a number 12 of -- particularly, the cohort studies, 13 particularly those that have information on 14 exposure that do indicate a connection between 15 dietary nitrosamines and cancer. I don't agree 16 with you. 17 Q. Okay. 18 Here, we're looking at an analysis of 19 cohort studies by an author of a paper that you 20 cited that says there's no association with NDMA 21 and gastric cancer. 22 A. Gastric cancer. 23 Q. And you agree with that? 24 A. What I said was that there are cohort 25 studies that show an association between NDMA and</p>
<p style="text-align: right;">Page 239</p> <p>1 You went a little quick again. Just 2 give me a second to object. 3 I object to the foundation of that 4 question. 5 Q. And Loh's work did not support and 6 cannot be cited for support for a statistical 7 association between NDMA and esophageal cancer, 8 correct? 9 A. Correct. 10 Q. Not only are the dietary study 11 results conflicting, but the authors of those 12 studies have even acknowledged that they're not 13 reliable in attempting to establish causation of 14 cancer, correct? 15 A. Where is that? 16 Q. I'm asking. I'm not saying it's in 17 this paper. I'm just asking -- 18 A. I haven't seen that they said it's 19 not reliable. Maybe you know where that is, but I 20 haven't seen it. Where the authors of the study 21 said their study was not reliable? I haven't seen 22 that. If they didn't think it was reliable, they 23 wouldn't try to publish it. 24 Q. The question that I was asking was a 25 little bit broader than that. I was simply asking</p>	<p style="text-align: right;">Page 241</p> <p>1 cancer, GI cancer. Not necessarily gastric 2 cancer. GI tract, colon, rectum -- 3 Q. Are you familiar with the -- 4 A. -- and others. 5 Q. -- song, S-O-N-G, paper? 6 A. Yes. 7 Q. It's entitled "Dietary Nitrates, 8 Nitrites and Nitrosamine Intake and the Risk of 9 Gastric Cancer, a Meta Analysis"? 10 A. Yes. 11 Q. What's a meta analysis? 12 A. Meta analysis, they combine data from 13 multiple different studies and combine them into 14 one statistical package that they use to do the 15 analysis. So it enables you to have a much larger 16 number of subjects than you would in a single 17 study. 18 Q. So Song pulled data from a lot of 19 different studies? 20 A. Yes. 21 Q. Isn't it true -- 22 A. Eleven studies. 23 Q. Okay. 24 Isn't it true that they -- that the 25 authors of the Song paper concluded that they</p>

<p style="text-align: right;">Page 242</p> <p>1 could not confirm the reliability of any 2 conclusions with respect to an association between 3 NDMA and cancer? 4 A. I have to look at it. I have to look 5 at it. 6 Q. It's up on the screen. We could go 7 to page 9893, if you'd like. 8 MR. SLATER: Hang on, Counsel. 9 Of course if Dr. Hecht wants to look 10 through the study before you continue, he's 11 allowed to, right? 12 MR. TRISCHLER: Of course. I was 13 just -- 14 MR. SLATER: I think that's what he 15 was doing. 16 MR. TRISCHLER: He could look if he 17 wants. He could read the whole thing if he'd 18 like. 19 MR. SLATER: Okay. 20 THE VIDEOGRAPHER: Counsel, sorry to 21 cut in. You didn't announce you were going 22 to mark this. Would you like this marked as 23 the next one? 24 MR. TRISCHLER: Sure. 25 (Whereupon, Exhibit 18 was marked for</p>	<p style="text-align: right;">Page 244</p> <p>1 the findings, which of course is applicable to 2 many epidemiologists, particularly diet and 3 cancer. 4 Q. Can we agree even though those 5 instances where a study notes or observes an 6 association that that association does not 7 establish causation? 8 MR. SLATER: Objection. 9 You can answer. 10 A. That depends on the study. I think 11 if we look at things like smoking and cancer and 12 UV and cancer where, you know, the relative risks 13 are extremely high, then you say yes, causation. 14 And, you know, you have to take into account all 15 of the data. So if we have a situation where 16 there's exposure to a carcinogen, which has 17 well-known carcinogenic effects on very low doses, 18 such as NDMA, and can be considered, it should be 19 regarded for practical purposes as if it were a 20 carcinogen to humans, then yes, that equals 21 causation. 22 Q. Let me be more specific. 23 Have you seen any paper published in 24 the literature that suggests that the -- that 25 there's a causal connection between exogenous NDMA</p>
<p style="text-align: right;">Page 243</p> <p>1 identification.) 2 THE VIDEOGRAPHER: This is Exhibit 3 18. 4 Do you want me to jump to 9893? 5 MR. TRISCHLER: He seems to be 6 reading it. If he wants you to, you can. 7 We'll let him read it -- 8 A. It's right in the abstract. The 9 summary relative risk of stomach cancer was 1.34 10 for NDMA. It's in the abstract. 11 Q. So you read the abstract? 12 A. I read the whole paper. 13 Q. I'm sorry? 14 A. Huh? 15 Q. I said you read the abstract, 16 correct? 17 A. I read the whole paper. 18 Q. All right. 19 Did you read the conclusion that 20 appears on page 9893? 21 A. Dietary nitrates intake was 22 associated with a reduced risk of gastric cancer 23 and high consumption of nitrites and NDMA could 24 increase the risk. They go on to say that they 25 could not absolutely confirm the reliability of</p>	<p style="text-align: right;">Page 245</p> <p>1 intake and the -- and the cause of cancer in 2 humans? 3 A. Yes. We just discussed -- what we've 4 been talking about the last hour. 5 Q. Show me where it says that these 6 exogenous NDMA intake in diet cause cancer. Where 7 does it say that, sir? 8 A. Causes cancer? 9 Q. Yes, that was the question. 10 A. No. The language is much more 11 cautious, of course. It has to be. 12 Q. I'm asking you has there ever been a 13 paper published where it's been concluded that 14 NDMA -- exogenous NDMA intake in food caused 15 cancer? 16 A. I would say collectively the papers 17 that we reviewed indicate that NDMA in food does 18 cause cancer. Otherwise, they wouldn't have seen 19 these elevated relative risks in all of these 20 different studies, some of which were very large. 21 Q. Show me a -- find me a statement in 22 any of the papers in your notebook where that 23 conclusion was made by an author of a published 24 study? 25 A. There isn't. That cause cancer?</p>

<p style="text-align: right;">Page 246</p> <p>1 Q. Right. It's not --</p> <p>2 A. It did not say that.</p> <p>3 Q. It's never been written in the</p> <p>4 scientific literature that dietary intake of NDMA</p> <p>5 has caused cancer; true?</p> <p>6 A. In humans.</p> <p>7 Q. In humans. Correct.</p> <p>8 A. Caused cancer, correct.</p> <p>9 Q. Never been --</p> <p>10 A. You can't --</p> <p>11 Q. Never been written --</p> <p>12 A. There's still not enough data to say</p> <p>13 absolutely cause cancer.</p> <p>14 Q. You've got to let me ask a question,</p> <p>15 sir.</p> <p>16 It's never been written anywhere in</p> <p>17 the scientific literature that dietary exposure to</p> <p>18 NDEA has caused cancer in humans, has it?</p> <p>19 A. Now you're on NDEA?</p> <p>20 Q. Yes.</p> <p>21 A. Okay. I thought you were talking</p> <p>22 about NDMA.</p> <p>23 I do not believe that there is such a</p> <p>24 study, yes, where it says NDEA caused cancer in</p> <p>25 humans. I don't think there is such a study in</p>	<p style="text-align: right;">Page 248</p> <p>1 Q. We've looked at a few, right?</p> <p>2 A. No. We looked at a number of</p> <p>3 different studies. You know, there are both</p> <p>4 positive and negative results depending on the</p> <p>5 tissue or organs being looked at and depending on</p> <p>6 the study. It's a mixed bag.</p> <p>7 Q. So since the dietary literature is a</p> <p>8 mixed bag, as you called it, what methodology did</p> <p>9 you employ to make the leap from an association</p> <p>10 between NDMA and cancer in some studies and</p> <p>11 causation?</p> <p>12 MR. SLATER: Objection.</p> <p>13 Foundation.</p> <p>14 You can answer.</p> <p>15 A. I take into consideration the high</p> <p>16 carcinogenicity of NDMA in animal models able to</p> <p>17 induce tumors and I think something like 28</p> <p>18 different animal species, even at very low doses</p> <p>19 as shown in rats. I combine that with the study</p> <p>20 design of the prospective studies and the very</p> <p>21 reliable dietary information on NDMA in food and I</p> <p>22 conclude that this is collectively a very strong</p> <p>23 link.</p> <p>24 Q. Are you familiar with the Bradford</p> <p>25 Hill criteria?</p>
<p style="text-align: right;">Page 247</p> <p>1 the literature.</p> <p>2 Q. Did you suggest to me and to this</p> <p>3 jury a little bit ago that the mere association</p> <p>4 between NDMA and cancer is enough to establish</p> <p>5 causation? Is that what you want us to believe?</p> <p>6 A. I'm saying that there are a number of</p> <p>7 strong studies where we have good solid dose</p> <p>8 information and we have good solid information on</p> <p>9 cancers that occurred and the study design is</p> <p>10 strong, such that collectively they present a</p> <p>11 conclusion that NDMA can cause cancer. Whether it</p> <p>12 does cause cancer, I would say it still needs</p> <p>13 research.</p> <p>14 Q. By the --</p> <p>15 A. I go back to this again.</p> <p>16 Q. By the same token --</p> <p>17 MR. SLATER: For the record, that was</p> <p>18 referring to the 1978 IARC publication?</p> <p>19 THE WITNESS: Yes.</p> <p>20 Q. By the same token, those same studies</p> <p>21 in the literature include many studies where there</p> <p>22 have been no association observed between NDMA and</p> <p>23 cancer, correct?</p> <p>24 A. I don't know about many. There are</p> <p>25 some.</p>	<p style="text-align: right;">Page 249</p> <p>1 A. Yes.</p> <p>2 Q. Do you recognize that the Bradford</p> <p>3 Hill criteria is a recognized methodology that's</p> <p>4 used to evaluate whether an observed association</p> <p>5 rises to the level of causation?</p> <p>6 A. Yes.</p> <p>7 Q. Are you familiar with the actual</p> <p>8 Bradford Hill criteria?</p> <p>9 A. Yes.</p> <p>10 Q. Can you cite any of them for me?</p> <p>11 A. I don't have them memorized, but we</p> <p>12 could pull it up if necessary.</p> <p>13 Q. It's not a memory test. I was just</p> <p>14 asking if you know any --</p> <p>15 A. Thank you.</p> <p>16 Q. -- offhand.</p> <p>17 A. Consistency is one of them.</p> <p>18 Q. There's nine of them total, right?</p> <p>19 A. I thought you said it wasn't a memory</p> <p>20 test.</p> <p>21 Q. It's not. I'm just asking if you</p> <p>22 know the number of them.</p> <p>23 A. So why don't you just pull it up then</p> <p>24 if you want to talk about it?</p> <p>25 Q. Did you employ the Bradford Hill</p>

<p style="text-align: right;">Page 250</p> <p>1 criteria in this case or utilize the Bradford Hill 2 criteria to determine whether the strength of 3 association in some of these studies merited 4 making the leap to causation? 5 A. No, I did not. 6 Q. Did you use any methodology that's 7 described in the scientific literature to assist 8 you in making your causation determination or was 9 it simply your own methodology? 10 A. I'm familiar with the methodology for 11 the analysis of nitrosamine in foods and I know 12 that there are very good, very thorough databases 13 on nitrosamines in food. 14 I'm familiar with the methodology 15 used in epidemiology prospective so-called cohort 16 studies. I'm familiar with those things and I'm 17 also familiar with the animal data on nitrosamines 18 and the dose response data for dimethyl and 19 several other nitrosamines from animal studies. 20 So I'm very familiar with all of this literature. 21 It doesn't -- it's not something that 22 I just started reading about, you know, to prepare 23 for this deposition. This is something I have 24 been involved with for more than 45 years, so I'm 25 quite familiar with the field. I watched the</p>	<p style="text-align: right;">Page 252</p> <p>1 methodology for making the leap from association 2 to causation? 3 A. It was not a formal -- 4 MR. SLATER: Objection. 5 One second, Doctor. Doctor, one 6 second. 7 Objection. That's a gross 8 mischaracterization and it's argumentative at 9 this point. 10 Do you want him to walk through his 11 methodology again for you, Counsel -- 12 MR. TRISCHLER: Sara, did you get the 13 answer? 14 MR. SLATER: Let me finish, please. 15 -- or do you want to keep saying 16 things regardless of what you heard? 17 MR. TRISCHLER: Sara, did you get the 18 answer? 19 (Whereupon, the record was read back 20 by the reporter.) 21 Q. Did you want to finish that answer, 22 Doctor? 23 A. It was not a formal evaluation. 24 Q. In your view of this case and based 25 on your knowledge of all the relevant literature</p>
<p style="text-align: right;">Page 251</p> <p>1 field evolve. I'm familiar with the evolution of 2 all of the animal data and the evolution of all of 3 the analytical chemistry data which in the early 4 days was plagued by artifacts and other problems, 5 but now is known to be extremely reliable. 6 So when I put all of this data 7 together and looking at it in comparison, looking 8 at it in context of the firm highly reliable data 9 that we have, put that together with the use of an 10 epidemiologic study design, with the cohort study, 11 I'm quite confident in the results of these 12 studies and after having reviewed them all, my 13 conclusion is that yes, there is definitely 14 causation. That's my conclusion. 15 Q. And your conclusion was based on the 16 fact that you're familiar with the literature and 17 you're familiar with nitrosamines, right? 18 A. More than familiar. I would say that 19 I have lived nitrosamines for more than half my 20 life. 21 Q. So you drew conclusions from the 22 literature based on your -- given that you're 23 familiar with it and experienced in the subject? 24 A. Yes. 25 Q. But you did not follow any recognized</p>	<p style="text-align: right;">Page 253</p> <p>1 which you've told us that you have, did you find a 2 single epidemiological study that concluded that 3 exogenous intake of NDMA was the cause of bladder 4 cancer in humans? 5 MR. SLATER: Objection. 6 A. Bladder cancer? I don't think I saw 7 bladder cancer. 8 Q. In your review -- 9 A. I don't think that's been reported. 10 Q. In your review of all the literature, 11 did you find a single peer review study that 12 concluded that exogenous intake of NDMA was the 13 cause of blood cancer in humans? 14 A. No. 15 Q. In your review of all the literature, 16 did you find a single peer-reviewed study that 17 concluded that exogenous intake of NDMA was the 18 cause of breast cancer in humans? 19 A. No. 20 Q. In your review of all the literature, 21 did you find a single peer-reviewed study that 22 concluded that exogenous intake of NDMA was the 23 cause of colorectal cancer in humans? 24 A. Yes. 25 Q. My question was cause, not</p>

<p style="text-align: right;">Page 254</p> <p>1 association.</p> <p>2 Did you find any papers that</p> <p>3 suggested that exogenous intake of NDMA was the</p> <p>4 cause of colorectal cancer in humans?</p> <p>5 A. We just reviewed -- we just did this.</p> <p>6 I mean, I don't know. I don't know what you're</p> <p>7 getting at here.</p> <p>8 Q. I'm distinguishing between --</p> <p>9 A. We just did this and we just</p> <p>10 discussed all of this, so I don't know what you're</p> <p>11 trying to get at.</p> <p>12 Q. Well, let me try and help you out, if</p> <p>13 I can. I'm distinguishing between a study that</p> <p>14 notes an association and a published study that</p> <p>15 makes a determination or statement regarding</p> <p>16 cause.</p> <p>17 So my question is are you aware of</p> <p>18 any peer-reviewed study that concluded that</p> <p>19 exogenous intake of NDMA was the cause of</p> <p>20 colorectal cancer in humans?</p> <p>21 A. No.</p> <p>22 Q. Are you aware of any published study</p> <p>23 that concluded that exogenous intake of NDMA was</p> <p>24 the cause of esophageal cancer in humans?</p> <p>25 A. No.</p>	<p style="text-align: right;">Page 256</p> <p>1 Q. Are you aware of any peer-reviewed</p> <p>2 study that concluded that exogenous intake was the</p> <p>3 cause of -- exogenous intake of NDMA was the cause</p> <p>4 of prostate cancer in humans?</p> <p>5 A. No.</p> <p>6 Q. Are you aware of any peer-reviewed</p> <p>7 study that concluded that the exogenous intake of</p> <p>8 NDMA was the cause of uterine cancer in humans?</p> <p>9 A. No.</p> <p>10 Q. I'm going to ask you a questions now</p> <p>11 about NDEA as opposed to NDMA.</p> <p>12 A. It's all the same answers. You don't</p> <p>13 have to go through it.</p> <p>14 Q. If we listed all 13 of the cancers</p> <p>15 that are at issue, are you aware of any</p> <p>16 peer-reviewed study that concluded that exogenous</p> <p>17 intake of NDEA was the cause of any of those</p> <p>18 cancers?</p> <p>19 A. No.</p> <p>20 Q. Do you agree or disagree with this</p> <p>21 statement, Doctor: DNA adduct formation alone is</p> <p>22 inadequate to confirm mutation or cancer?</p> <p>23 A. Agree.</p> <p>24 MR. SLATER: Objection.</p> <p>25 You went a little quick again.</p>
<p style="text-align: right;">Page 255</p> <p>1 Q. Are you aware of any peer-reviewed</p> <p>2 published study that concluded that exogenous</p> <p>3 intake of NDMA was the cause of gastric cancer in</p> <p>4 humans?</p> <p>5 A. Cause? No.</p> <p>6 Q. Are you aware of any peer-reviewed</p> <p>7 study that concluded that exogenous intake of NDMA</p> <p>8 was the cause of kidney cancer in humans?</p> <p>9 A. No.</p> <p>10 Q. Are you aware of any peer-reviewed</p> <p>11 study that concluded that exogenous intake of NDMA</p> <p>12 was the cause of liver cancer in humans?</p> <p>13 A. No.</p> <p>14 Q. Are you aware of any peer-reviewed</p> <p>15 studies that concluded that exogenous intake of</p> <p>16 NDMA was the cause of lung cancer in humans?</p> <p>17 A. No. Not cause, no.</p> <p>18 Q. Are you aware of any peer-reviewed</p> <p>19 study that concluded that exogenous intake of NDMA</p> <p>20 was the cause of pancreatic cancer in humans?</p> <p>21 A. No.</p> <p>22 Q. Are you aware of any peer-reviewed</p> <p>23 study that concluded that the exogenous intake of</p> <p>24 NDMA was the cause of pharyngeal cancer in humans?</p> <p>25 A. No.</p>	<p style="text-align: right;">Page 257</p> <p>1 Are we going back over this again? I</p> <p>2 thought we --</p> <p>3 MR. TRISCHLER: You cut out, Adam. I</p> <p>4 couldn't hear you.</p> <p>5 MR. SLATER: Can you hear me now?</p> <p>6 MR. TRISCHLER: Yes.</p> <p>7 MR. SLATER: I said objection.</p> <p>8 I thought we covered this hours ago.</p> <p>9 Q. Are you familiar with MGMT?</p> <p>10 A. Yes.</p> <p>11 Q. Is MGMT a DNA repair enzyme?</p> <p>12 A. Yes.</p> <p>13 Q. Is it one of those things in our body</p> <p>14 that allows us to fight off mutagens?</p> <p>15 A. No, it doesn't act on mutagens. It</p> <p>16 acts on DNA adducts, specifically</p> <p>17 O6-methylguanine. So O6-methylguanine DNA methyl</p> <p>18 transfers. Therefore the name MGMT.</p> <p>19 Q. Do you agree or disagree with this</p> <p>20 statement: Risks from nitrosamines in drugs is</p> <p>21 likely to be very low because depletion of MGMT is</p> <p>22 not expected?</p> <p>23 A. I don't necessarily agree with that,</p> <p>24 no.</p> <p>25 Q. What would be your --</p>

<p style="text-align: right;">Page 258</p> <p>1 A. I don't agree with that.</p> <p>2 Q. What would be your basis for</p> <p>3 disagreeing?</p> <p>4 A. Well, MGMT activity might be low for</p> <p>5 a number of reasons. It may have been MGMT</p> <p>6 activity may have been used up by other exposures,</p> <p>7 so, you know, if there is O6-alkylguanine form</p> <p>8 from various different exposures, some of which we</p> <p>9 may not be aware of, MGMT can be used up tending</p> <p>10 to those exposures.</p> <p>11 Q. Do you --</p> <p>12 A. So I don't think we know -- we don't</p> <p>13 really know, you know, how much MGMT activity a</p> <p>14 person has in reserve to address nitrosamine</p> <p>15 exposure. We don't have that information.</p> <p>16 Q. So long as there's no MGMT depletion,</p> <p>17 one would not expect that a low-level nitrosamine</p> <p>18 exposure would lead to the development of</p> <p>19 mutagens, correct?</p> <p>20 MR. SLATER: Objection.</p> <p>21 You can answer.</p> <p>22 A. No, I don't think that's correct. I</p> <p>23 mean, nitrosamines do a lot of things to DNA.</p> <p>24 It's not just O6-methylguanine.</p> <p>25 Dimethylnitrosamine forms multiple different</p>	<p style="text-align: right;">Page 260</p> <p>1 A. Okay.</p> <p>2 Q. You -- we talked about how you were</p> <p>3 retained by --</p> <p>4 MR. SLATER: Counsel, excuse me, I</p> <p>5 don't mean to interrupt, but are you now</p> <p>6 going to rehash the testimony from six hours</p> <p>7 ago? I don't understand what we're doing.</p> <p>8 MR. TRISCHLER: You probably couldn't</p> <p>9 understand what I'm doing since I haven't</p> <p>10 asked a question yet.</p> <p>11 MR. SLATER: Well, no, but you</p> <p>12 started to ask about, you know, you're back</p> <p>13 to the beginning. I don't think it's a</p> <p>14 reasonable predicate to say "Well, I just</p> <p>15 want to make sure I understand ..." and then</p> <p>16 go over testimony you took in great detail in</p> <p>17 the questioning. I ask you not to duplicate</p> <p>18 that questioning, please.</p> <p>19 MR. TRISCHLER: Well, since I haven't</p> <p>20 asked a question yet, I don't know how it</p> <p>21 could be duplicative, but if you think it is,</p> <p>22 I'm sure you could object to it on that</p> <p>23 basis.</p> <p>24 MR. SLATER: Well, it's your</p> <p>25 obligation not to do so, so don't put it on</p>
<p style="text-align: right;">Page 259</p> <p>1 adducts in DNA. O6-methylguanine has been studied</p> <p>2 most extensively because we know that it has</p> <p>3 miscoding properties. We know that it can lead to</p> <p>4 mutations. We know about MGMT, we know that it's</p> <p>5 -- well, it's not the major DNA damage caused by</p> <p>6 nitrosamines by any means. It's actually one of</p> <p>7 the minor ones. So there's a lot of other damaged</p> <p>8 DNA that can lead to mutations and cancer. It</p> <p>9 wouldn't be addressed by MGMT.</p> <p>10 Q. Have you ever studied MGMT depletion</p> <p>11 in humans?</p> <p>12 A. No, I honestly have not studied it.</p> <p>13 My group has not studied it. There's a fair</p> <p>14 amount of literature on it. There's a large</p> <p>15 amount of literature on it, particularly in the</p> <p>16 chemotherapy literature because MGMT can act on</p> <p>17 chemotherapeutic drugs, decreasing their efficacy,</p> <p>18 so people looked for inhibitors of MGMT to be used</p> <p>19 as co-factors in chemotherapy.</p> <p>20 Q. I want to go back and do a little</p> <p>21 housekeeping, just to make sure that I have an</p> <p>22 understanding of everything that you reviewed and</p> <p>23 relied upon to put together your report and come</p> <p>24 to your conclusions.</p> <p>25 Okay?</p>	<p style="text-align: right;">Page 261</p> <p>1 me, please.</p> <p>2 Q. You told us that you reviewed</p> <p>3 documents that were provided to you by counsel.</p> <p>4 Do you recall that?</p> <p>5 A. Yes.</p> <p>6 MR. TRISCHLER: I'm going to mark as</p> <p>7 an exhibit the next number that we're up to,</p> <p>8 a document that I think was attached to your</p> <p>9 report. It's called "Documents Reviewed" and</p> <p>10 it's Exhibit 2 to your report. I'm going to</p> <p>11 mark it as a separate exhibit here.</p> <p>12 Can you put that up, Bill, please?</p> <p>13 THE VIDEOGRAPHER: Just looking for a</p> <p>14 document that matches that description.</p> <p>15 Just give me one moment.</p> <p>16 THE WITNESS: It's B. It's addendum</p> <p>17 B.</p> <p>18 THE VIDEOGRAPHER: I'm seeing a</p> <p>19 document that was uploaded. The name of the</p> <p>20 document is reviewed -- got it. Sorry about</p> <p>21 that. That will be Exhibit 19.</p> <p>22 (Whereupon, Exhibit 19 was marked for</p> <p>23 identification.)</p> <p>24 Q. This is a document that you prepared</p> <p>25 and provided in connection with your report,</p>

<p style="text-align: right;">Page 262</p> <p>1 correct, sir?</p> <p>2 A. Yes.</p> <p>3 Q. All I'm trying to confirm is is this</p> <p>4 a list of documents that were provided to you by</p> <p>5 counsel in connection with your review and your</p> <p>6 work in this case?</p> <p>7 A. Yes.</p> <p>8 Q. I think that -- and to be fair, when</p> <p>9 we get to the last -- the second-to-last page,</p> <p>10 there's a section marked "Regulatory Documents"</p> <p>11 and you had indicated before that, you know, in</p> <p>12 addition to looking at company documents and the</p> <p>13 public literature, you also looked at public</p> <p>14 materials about the valsartan medications,</p> <p>15 correct?</p> <p>16 A. Yes.</p> <p>17 Q. Would this be a list of those public</p> <p>18 documents that you reviewed?</p> <p>19 A. Yes.</p> <p>20 Q. Is there -- other than what's on this</p> <p>21 six-page list -- and please feel free to go</p> <p>22 through it if you need -- but are there any other</p> <p>23 documents that you reviewed or received in</p> <p>24 connection with your work in this case prior to</p> <p>25 the time you sat down and wrote the report that we</p>	<p style="text-align: right;">Page 264</p> <p>1 reference of what the contents of his file</p> <p>2 were, so I was going to mark them as a</p> <p>3 numbered exhibit, if that's okay.</p> <p>4 MR. SLATER: Well, yeah, I'm not</p> <p>5 going to tell you that's all the materials in</p> <p>6 his file, though, because I don't know that</p> <p>7 it is. I don't think it is. I don't think</p> <p>8 we printed everything. So I don't think</p> <p>9 that's going to -- his file is -- I mean, you</p> <p>10 have everything. I just can't tell you those</p> <p>11 table of contents is everything because I</p> <p>12 don't think we sent him everything.</p> <p>13 MR. TRISCHLER: Fair enough.</p> <p>14 (Whereupon, Exhibit 20 was marked for</p> <p>15 identification.)</p> <p>16 BY MR. TRISCHLER:</p> <p>17 Q. Dr. Hecht, I'm just trying to -- what</p> <p>18 I'm obviously interested is in knowing everything</p> <p>19 you may have read, reviewed and relied upon.</p> <p>20 Do you have the tables of contents</p> <p>21 for the binders in front of you?</p> <p>22 A. Yes.</p> <p>23 Q. Can you take a look at those and tell</p> <p>24 me whether those tables of contents contain the</p> <p>25 documents and literature that you relied upon?</p>
<p style="text-align: right;">Page 263</p> <p>1 marked as Exhibit 1?</p> <p>2 A. No. The list is complete.</p> <p>3 Q. I was told that you also -- it was</p> <p>4 delivered to me yesterday, six binders of</p> <p>5 materials that was delivered to me electronically</p> <p>6 and there was a table of contents with those</p> <p>7 binders.</p> <p>8 Have you ever seen those tables of</p> <p>9 contents?</p> <p>10 A. I think I know what you're referring</p> <p>11 to. I mean, in the binders, the binders have a</p> <p>12 table of contents.</p> <p>13 MR. TRISCHLER: I don't know if we</p> <p>14 have these in the chat or available, but I</p> <p>15 was going to mark the table of contents in</p> <p>16 the binder as the next number of exhibit,</p> <p>17 just so we have a record of what his file</p> <p>18 materials consist of. Okay?</p> <p>19 MR. SLATER: Yeah, I mean all those</p> <p>20 materials you have already and have had.</p> <p>21 Those were just provided to him for his</p> <p>22 convenience, in case he wanted to look at</p> <p>23 them. You can mark them --</p> <p>24 MR. TRISCHLER: Right. I understand</p> <p>25 that. I understand, but it's a nice handy</p>	<p style="text-align: right;">Page 265</p> <p>1 MR. SLATER: I'm sorry, Clem. You're</p> <p>2 asking him to do it? He's going to have to</p> <p>3 sit there and walk through it, compare it to</p> <p>4 the "Materials Reviewed" list and his whole</p> <p>5 report? Is that what you're asking him to</p> <p>6 do?</p> <p>7 MR. TRISCHLER: I don't really want</p> <p>8 him to do that, Adam --</p> <p>9 MR. SLATER: But, I mean, you have it</p> <p>10 attached to the report, you have the</p> <p>11 references in the report, so you can mark the</p> <p>12 tables of contents, you can do whatever you</p> <p>13 want, I'm just not really sure what we're</p> <p>14 getting at. You have the tables of contents.</p> <p>15 Is there something on those tables of</p> <p>16 contents that you think wasn't in the report?</p> <p>17 You can tell us and ask him the question, but</p> <p>18 I don't think so.</p> <p>19 MR. TRISCHLER: I guess that's the</p> <p>20 question. Let me ask that question.</p> <p>21 Q. Do you know if there's anything</p> <p>22 listed on the tables of contents in these binders</p> <p>23 that were not cited in your report?</p> <p>24 MR. SLATER: You want him -- you want</p> <p>25 him to go through and compare everything? I</p>

<p style="text-align: right;">Page 266</p> <p>1 mean, I'm told by Chris that he thinks that</p> <p>2 the tables of contents are pretty</p> <p>3 comprehensive, if not everything. But I just</p> <p>4 can't swear to it right now. Short of him</p> <p>5 comparing everything, how else is he going to</p> <p>6 be sure?</p> <p>7 MR. TRISCHLER: I didn't get the</p> <p>8 binders until yesterday. I didn't get a</p> <p>9 chance to look at them. I'm just trying --</p> <p>10 MR. SLATER: Clem, we gave those</p> <p>11 binders as a courtesy because they're not new</p> <p>12 materials. They're all things you already</p> <p>13 had.</p> <p>14 MR. TRISCHLER: And I'm not</p> <p>15 complaining, Adam. I'm trying to figure out</p> <p>16 whether there's anything on here that I</p> <p>17 haven't seen or hasn't been identified</p> <p>18 before. I don't think that's an improper</p> <p>19 question.</p> <p>20 MR. SLATER: No, but I'm saying</p> <p>21 wouldn't it be easier to have someone in your</p> <p>22 office go down the list and compare to the</p> <p>23 report and see if there's anything new?</p> <p>24 MR. TRISCHLER: Well, perhaps, but I</p> <p>25 wasn't smart enough to do that.</p>	<p style="text-align: right;">Page 268</p> <p>1 know.</p> <p>2 Thank you.</p> <p>3 BY MR. TRISCHLER:</p> <p>4 Q. Do you know offhand, Doctor -- and I</p> <p>5 don't know how much time you spent with the</p> <p>6 binder -- do you know offhand whether there's</p> <p>7 anything in the binders that is not identified in</p> <p>8 the documents reviewed that we marked as the last</p> <p>9 exhibit and the references that are mentioned in</p> <p>10 the report?</p> <p>11 A. No. I mean, offhand, you know, the</p> <p>12 binders contain what's in the report.</p> <p>13 Q. Is there any work that you've done</p> <p>14 since preparing your report in this case?</p> <p>15 A. What do you mean by work?</p> <p>16 Q. Well, I mean --</p> <p>17 A. I had to review all of the material.</p> <p>18 I mean, that's work.</p> <p>19 Q. Sure. Fair enough.</p> <p>20 Other than reviewing the material, is</p> <p>21 there any new work that you did, any new studies</p> <p>22 that you looked at, any additional research that</p> <p>23 you've done since you wrote this report in July?</p> <p>24 A. No. Not relevant to this case.</p> <p>25 Q. As part of your work in this case,</p>
<p style="text-align: right;">Page 267</p> <p>1 MR. SLATER: That's not -- I'm not</p> <p>2 being nasty, so I don't need that comment.</p> <p>3 MR. TRISCHLER: I didn't suggest you</p> <p>4 were being nasty.</p> <p>5 MR. SLATER: Look, you use the time</p> <p>6 any way you want.</p> <p>7 Do you know yet if anyone else plans</p> <p>8 to follow up after you because we are</p> <p>9 probably at seven hours now?</p> <p>10 MR. TRISCHLER: I don't how long</p> <p>11 we're into it and I don't know the answer to</p> <p>12 that question, but let's just see if we could</p> <p>13 get this done and then we'll move on to</p> <p>14 something else.</p> <p>15 THE VIDEOGRAPHER: Counsel, sorry to</p> <p>16 cut it. Just to let you know, I don't have</p> <p>17 a document, the table of contents --</p> <p>18 MR. TRISCHLER: I know you don't. I</p> <p>19 already said that you don't have it.</p> <p>20 THE VIDEOGRAPHER: I'm saying if you</p> <p>21 want to send it to me later on, I can mark</p> <p>22 that as the next exhibit.</p> <p>23 MR. TRISCHLER: Right.</p> <p>24 THE VIDEOGRAPHER: And we have about</p> <p>25 seven minutes on this media, just so you</p>	<p style="text-align: right;">Page 269</p> <p>1 have you reviewed the reports of other experts</p> <p>2 that were retained by the plaintiffs in this</p> <p>3 litigation?</p> <p>4 A. No, not the reports. I did see some</p> <p>5 transcripts of, you know, parts of testimony, but</p> <p>6 not -- I didn't review the report, I haven't</p> <p>7 reviewed any of the reports.</p> <p>8 Q. I'll represent to you that the</p> <p>9 depositions of the experts for the plaintiff are</p> <p>10 only taking place recently, so that's including</p> <p>11 your deposition obviously.</p> <p>12 I'm looking at the list of deposition</p> <p>13 testimony that you reviewed that's part of our</p> <p>14 last numbered exhibit and --</p> <p>15 A. No, I didn't review those. I don't</p> <p>16 know why that's there. I haven't seen them. I</p> <p>17 haven't seen those.</p> <p>18 MR. SLATER: Dr. Hecht, can you wait</p> <p>19 until he asks you a question, please? He</p> <p>20 hasn't asked you yet. He's moved off the</p> <p>21 expert reports. He's onto something new now.</p> <p>22 Q. You've not reviewed any expert</p> <p>23 reports from any other expert in the case; true?</p> <p>24 A. No. True.</p> <p>25 Q. You've not seen any of the deposition</p>

<p style="text-align: right;">Page 270</p> <p>1 transcripts from any of the experts in the case?</p> <p>2 A. Correct.</p> <p>3 Q. You've not spoken to any of the other</p> <p>4 experts retained by plaintiff?</p> <p>5 A. Correct.</p> <p>6 Q. And I take it that you're not relying</p> <p>7 upon any other expert retained by plaintiff to</p> <p>8 support any of your opinions in this case?</p> <p>9 A. Correct.</p> <p>10 Q. I asked you before about medical</p> <p>11 records and you told me you haven't reviewed any</p> <p>12 patient medical records.</p> <p>13 Have you reviewed any pathology</p> <p>14 slides or tissue samples for any plaintiff?</p> <p>15 A. No.</p> <p>16 Q. Have you reviewed any of the reports</p> <p>17 of any of the defense experts in this case?</p> <p>18 A. No.</p> <p>19 Q. Do you know who any of the defense</p> <p>20 experts are?</p> <p>21 A. No, I do not.</p> <p>22 Q. When's the last time you gave a</p> <p>23 deposition or sworn testimony under oath?</p> <p>24 A. Repeat the question, please. I</p> <p>25 didn't hear the whole thing.</p>	<p style="text-align: right;">Page 272</p> <p>1 time for me to go into another area and I'm</p> <p>2 getting near completion.</p> <p>3 Can we take a five-minute break,</p> <p>4 Adam, and if you want, I can roundtable with</p> <p>5 my colleagues and see who we have as</p> <p>6 questioning and how much?</p> <p>7 MR. SLATER: Okay. Obviously with</p> <p>8 the caution that there shouldn't be any</p> <p>9 duplicative questioning obviously.</p> <p>10 That's not for your benefit --</p> <p>11 MR. TRISCHLER: I don't think any</p> <p>12 that's the intent of anybody, but I</p> <p>13 understand your position.</p> <p>14 Why don't we take ten minutes? It'll</p> <p>15 give me a chance to look at the rest of what</p> <p>16 I want to do and then I can get some -- at</p> <p>17 least some electronic feedback from our side</p> <p>18 as to what else people think.</p> <p>19 Okay?</p> <p>20 MR. SLATER: Sounds good.</p> <p>21 THE VIDEOGRAPHER: The time is 4:27.</p> <p>22 This concludes media four.</p> <p>23 (Recess taken)</p> <p>24 THE VIDEOGRAPHER: The time is now</p> <p>25 4:38.</p>
<p style="text-align: right;">Page 271</p> <p>1 Q. Sure.</p> <p>2 When's the last time you gave a</p> <p>3 deposition or other sworn testimony under oath?</p> <p>4 A. I don't remember the exact date, but</p> <p>5 I believe it was about ten years ago in a case</p> <p>6 involving smokeless tobacco and cancer. I'm not</p> <p>7 sure of the exact date.</p> <p>8 Q. Were you working as an expert witness</p> <p>9 in this case ten years ago?</p> <p>10 A. Yes.</p> <p>11 Q. In connection with your expert work</p> <p>12 where you've been asked to give depositions or</p> <p>13 give deposition testimony, has all of it been in</p> <p>14 cases involving tobacco?</p> <p>15 A. Yes.</p> <p>16 Q. I guess another way of asking the</p> <p>17 same question, just to make sure I understand and</p> <p>18 get the complete answer, have you ever been</p> <p>19 involved in a litigation matter as an expert</p> <p>20 witness that did not involve tobacco?</p> <p>21 A. No.</p> <p>22 Q. Have you ever testified at trial as</p> <p>23 an expert witness?</p> <p>24 A. No. No.</p> <p>25 MR. TRISCHLER: This would be a good</p>	<p style="text-align: right;">Page 273</p> <p>1 This begins media five.</p> <p>2 You may proceed.</p> <p>3 Q. Dr. Hecht, are you familiar with the</p> <p>4 Pottegård study?</p> <p>5 A. Pottegård?</p> <p>6 MR. SLATER: Which study did you say,</p> <p>7 Clem? I missed that.</p> <p>8 MR. TRISCHLER: Pottegård.</p> <p>9 A. I am.</p> <p>10 Q. I'll give you a second to grab</p> <p>11 whatever you're looking for. Are you pulling up a</p> <p>12 copy of the study?</p> <p>13 A. Yeah, I am.</p> <p>14 Okay. That's the Danish --</p> <p>15 (Whereupon, Exhibit 21 was marked for</p> <p>16 identification.)</p> <p>17 Q. Right. Yes, sir. We'll mark the</p> <p>18 Pottegård study as the next numbered exhibit. You</p> <p>19 don't have to show it. The witness has it in</p> <p>20 front of him.</p> <p>21 In this Pottegård paper, the authors</p> <p>22 followed about 5,150 Danish patients who used</p> <p>23 valsartan, correct?</p> <p>24 A. Yes.</p> <p>25 Q. And I think what the paper tells us</p>

<p style="text-align: right;">Page 274</p> <p>1 is that the scientists who did this study followed 2 these individuals for a median of 4.6 years and 3 examined cancer rates in valsartan users as 4 compared to a cohort of non-valsartan users, 5 right? 6 A. Yes. 7 Q. Based on your review of this study, 8 was it a good, well-designed study? 9 A. Well, you know, the follow up -- the 10 sample size was pretty small and the follow up is 11 also pretty small. So I mean as an initial pass 12 at the problem, and, you know, the effects of the 13 NDMA in tablets, I guess it was okay. But, I 14 mean, it's a relatively small study and the follow 15 up is not very long, so it's not too surprising 16 that it didn't find anything. So, you know, a 17 negative study doesn't really prove anything. 18 Q. So as with all studies, there were 19 some limitations to it? 20 A. I wouldn't say all studies. That's a 21 very broad statement. 22 Q. I thought you said that all studies 23 have limitations? 24 A. Maybe I said that, but not all 25 studies. Well, all studies have some limitations.</p>	<p style="text-align: right;">Page 276</p> <p>1 going to be filed with the court? 2 A. Yes. 3 Q. And did you put together the report 4 as a summary of the scientific basis for the 5 opinions that you were offering? 6 A. Yes. 7 Q. Do you agree that a report of this 8 nature should not misstate or misrepresent the 9 state of clients as reflected in the literature? 10 A. Yes. 11 Q. I assume you'd agree with me that 12 scientists are not supposed to take liberties in 13 preparing reports of this nature, correct? 14 A. I don't know what you mean by "take 15 liberties." 16 Q. Well, stretching the truth or 17 distorting findings is not what a scientist is 18 supposed to do. 19 Can we agree on that? 20 A. We never stretch the truth or distort 21 findings. 22 Q. And so when you cite to Pottegård in 23 your report -- strike that. 24 When you put this report together, 25 you already told me that one of the questions that</p>
<p style="text-align: right;">Page 275</p> <p>1 I guess that's true. It's a very broad statement. 2 We do experimental studies here that 3 I don't really think have any limitations. When 4 you're talking about studies of populations, then 5 the limitations become more -- there can be more 6 limitations. 7 Q. In any event, what Pottegård reported 8 was that there was no evidence of a markedly 9 increased short term overall risk of cancer from 10 the valsartan containing NDMA, correct? 11 A. Yes. 12 Q. You cite Pottegård in your report 13 that you prepared for this case, right? 14 A. Yes. 15 Q. And when you prepared this report 16 back in July, did you understand that it was going 17 to be filed with the Federal MDL Court? 18 A. Federal MDL Court is what? 19 Q. That's the court -- 20 A. I don't think so. I'm not sure I 21 know what you're talking about. 22 Q. I'm trying to tell you, explain it to 23 you. 24 It's the court where this litigation 25 is based. Did you understand that this report was</p>	<p style="text-align: right;">Page 277</p> <p>1 was at the heart of this was whether or not NDMA 2 can cause cancer in humans, correct? 3 A. Yes. 4 Q. So when you cite to -- here, we have 5 a study like Pottegård that aims to answer that 6 very question, right? 7 A. Yes. 8 Q. When you cite to Pottegård in your 9 report, you make no mention at all of the authors' 10 conclusion that NDMA in valsartan was not found to 11 increase the short term overall risk of cancer? 12 A. No. 13 Q. Right? Never mention that? 14 MR. SLATER: Objection. 15 You can answer. 16 A. That's what you say. 17 Q. Well, it's what I say, but it's 18 truthful, right? You never mention it in your 19 report -- 20 A. Okay. 21 Q. -- what Pottegård included? 22 A. All right. That's an oversight. I 23 should have mentioned it. 24 Q. Because that's an important 25 observation obviously, right?</p>

<p style="text-align: right;">Page 278</p> <p>1 MR. SLATER: Objection.</p> <p>2 A. It's a preliminary observation. I</p> <p>3 don't know if it's really an important</p> <p>4 observation.</p> <p>5 Q. It's something an objective scientist</p> <p>6 would want to disclose, don't you think?</p> <p>7 MR. SLATER: Objection.</p> <p>8 Wait. Time out, Dr. Hecht.</p> <p>9 Objection.</p> <p>10 Argumentative.</p> <p>11 Do you have a question, rather than</p> <p>12 just making statements at the witness?</p> <p>13 MR. TRISCHLER: I just asked it and</p> <p>14 he just answered it.</p> <p>15 MR. SLATER: Yeah, but you didn't</p> <p>16 ask. You're just throwing statements at him</p> <p>17 instead of asking the question.</p> <p>18 Do you have a question about</p> <p>19 Pottegård? Do you have a question about</p> <p>20 something?</p> <p>21 MR. TRISCHLER: I have another one</p> <p>22 that I'll ask as soon as you're done.</p> <p>23 BY MR. TRISCHLER:</p> <p>24 Q. Why did you omit Pottegård's</p> <p>25 conclusion that there was no short term overall</p>	<p style="text-align: right;">Page 280</p> <p>1 it more.</p> <p>2 Q. Well, what you did cite to with</p> <p>3 respect to Pottegård was you make a suggestion at</p> <p>4 page 16 that the study found an increased risk for</p> <p>5 colorectal cancer and uterine cancer.</p> <p>6 Do you see that at page 16?</p> <p>7 A. Yes, I see that.</p> <p>8 MR. SLATER: That's the only</p> <p>9 question, Doctor. Did you --</p> <p>10 A. I'm a little puzzled by that.</p> <p>11 Q. Is that an accurate statement? Is</p> <p>12 that what Pottegård actually found?</p> <p>13 A. In the analysis of single cancer</p> <p>14 outcomes, increased risks were seen for colorectal</p> <p>15 cancer and for uterine cancer, although neither</p> <p>16 these, nor other single cancer outcomes reached</p> <p>17 statistical significance.</p> <p>18 So yeah, that was the outcome. It</p> <p>19 wasn't -- so it's -- it's not exactly right,</p> <p>20 what's written here. It's a little unclear. It's</p> <p>21 not that clear.</p> <p>22 Q. "Not exactly right" --</p> <p>23 A. I should have -- I should have -- I</p> <p>24 should have been more clear in the way I wrote</p> <p>25 this.</p>
<p style="text-align: right;">Page 279</p> <p>1 risk of cancer associated with the use of</p> <p>2 valsartan with NDMA from your report?</p> <p>3 MR. SLATER: Objection to the</p> <p>4 terminology and foundation.</p> <p>5 You can answer.</p> <p>6 A. I guess I have to find the page where</p> <p>7 the --</p> <p>8 Q. Sure. I can help you --</p> <p>9 A. -- Pottegård is discussed, so I see</p> <p>10 exactly what I said here. What page is it?</p> <p>11 Q. Page 16 is where I see it, both in</p> <p>12 the first full paragraph and the last.</p> <p>13 A. Yeah, I summarize the EMA comments.</p> <p>14 EMA statement cites and discusses a study</p> <p>15 performed in Denmark. That's the Pottegård study.</p> <p>16 I'm a little confused here. Yeah.</p> <p>17 So what's your question? What is your question?</p> <p>18 Q. Why did you make no mention of</p> <p>19 Pottegård's conclusion that NDMA in valsartan did</p> <p>20 not lead to an increased short term overall risk</p> <p>21 of cancer?</p> <p>22 A. Well, I guess I took the NDMA</p> <p>23 valuation of the 4.6 year follow-up interval was</p> <p>24 likely too short, so I didn't discuss it further</p> <p>25 than that. I might have -- might have discussed</p>	<p style="text-align: right;">Page 281</p> <p>1 Q. "Not exactly right" is a kind way of</p> <p>2 saying what you wrote is incorrect?</p> <p>3 MR. SLATER: Objection.</p> <p>4 Q. If you look at the results on the</p> <p>5 first page of the study, what Pottegård wrote was</p> <p>6 that the confidence intervals for the single</p> <p>7 outcome cancers were so wide as to include the</p> <p>8 null, so no conclusions could be drawn, right?</p> <p>9 A. Yes.</p> <p>10 Q. Looking at it now, what we can say is</p> <p>11 that Pottegård never found a statistically</p> <p>12 significant increased risk of colorectal cancer,</p> <p>13 did he?</p> <p>14 A. No.</p> <p>15 Q. He never found a statistically</p> <p>16 significant increased risk of uterine cancer, did</p> <p>17 he?</p> <p>18 A. That's correct.</p> <p>19 Q. Those are obviously important</p> <p>20 observations that were never mentioned in your</p> <p>21 report either, correct?</p> <p>22 MR. SLATER: Objection.</p> <p>23 You can answer.</p> <p>24 A. It's an oversight that should have</p> <p>25 been mentioned.</p>

<p style="text-align: right;">Page 282</p> <p>1 Q. You also cite to the Gomm study in 2 your report on page 16, right? 3 A. Yes. 4 Q. Do you have that with you, sir, and 5 available to you? 6 A. I do. 7 MR. TRISCHLER: We'll mark the Gomm 8 study the next numbered exhibit. 9 Bill, you do not have to display it 10 since the witness has it in front of him. 11 (Whereupon, Exhibit 22 was marked for 12 identification.) 13 Q. Doctor, Gomm was a study where they 14 used the German registry database to look at over 15 750,000 individuals who filled valsartan scripts, 16 right? 17 A. Yes. 18 Q. And the incidence of cancer was 19 compared to non-valsartan users, right? 20 A. Yes. 21 Q. And we talked about how most every 22 study has limits and I assume Gomm is no 23 exception, right? 24 A. Sure. 25 Q. But not withstanding those limits,</p>	<p style="text-align: right;">Page 284</p> <p>1 both -- really, they're both preliminary studies. 2 The follow up would have to be longer and we would 3 need to know more about who actually took which 4 pills, which is not addressed here. 5 So, you know, these are -- I think 6 these are okay as preliminary studies, but I think 7 they're both preliminary. We need -- we would 8 need a -- more of a follow up, for example, you 9 wouldn't really necessarily expect to see an 10 increase in liver cancer within three years. 11 And the same goes for the other 12 study. I think the follow-up time is too short 13 and there are many -- there's many questions about 14 both of these studies. 15 Q. All right. 16 Limitations aside, you would agree 17 with me we do have two nationwide studies which 18 both reported no increase in the overall risk of 19 cancer. 20 Agreed? 21 A. Yes, but I wouldn't put the 22 limitations aside. Limitations are there. It's 23 obvious what they are. 24 Q. In your report -- 25 A. I don't think you would expect an</p>
<p style="text-align: right;">Page 283</p> <p>1 did you find Gomm to be a good study? 2 A. I found out to be remarkable in the 3 sense that they sought excessive liver cancer. 4 Q. Did you find the conclusions in this 5 study reliable? 6 A. Yes, but it needs confirmation. 7 Q. Gomm reached the same conclusion as 8 Pottegård. In a national study, there was no 9 evidence of an increase in the overall risk of 10 cancer amongst valsartan users, correct? 11 A. Overall, yeah. But they did find a 12 risk -- an increased risk of liver cancer. 13 Q. We'll talk about that in a minute. 14 In terms of the overall risk of 15 cancer, Gomm found no evidence of such an 16 increased risk; true? 17 A. Correct. 18 Q. The conclusion is Pottegård, correct? 19 A. Yes. 20 Q. So we have two national studies done 21 by two different groups of scientists, both 22 concluding that NDMA in valsartan did not lead to 23 an increased overall risk of cancer; true? 24 A. Well, I think the follow up would 25 have to be much longer. You know, these are</p>	<p style="text-align: right;">Page 285</p> <p>1 increased incidence of liver cancer within three 2 years. 3 Q. In your report to this court where 4 you tried to honestly and objectively answer the 5 causation question, you never mentioned the 6 findings of either one of these studies, right? 7 MR. SLATER: Objection. 8 A. No, they're both in the report. 9 Q. No, they're not. We went through it. 10 You don't mention -- 11 MR. SLATER: Counselor, lower your 12 voice towards the witness and look at the 13 page because he just told you it's in the 14 report. You obviously haven't read page 16. 15 You're not going to attack him 16 aggressively like this. You're not going to 17 do it. You're just not going to do it. 18 Q. Sir, do you ever mention in your 19 report that Pottegård found no overall increased 20 risk of cancer? Yes or no? 21 MR. SLATER: Objection. 22 We went through this already. 23 You can answer again. 24 A. Pottegård? We already went through 25 this. Pottegård did not find a significant</p>

<p style="text-align: right;">Page 286</p> <p>1 increase.</p> <p>2 Q. Correct.</p> <p>3 Am I correct --</p> <p>4 A. Did not find -- did not find a</p> <p>5 significant increase.</p> <p>6 Q. Correct.</p> <p>7 My question is did you ever mention</p> <p>8 that in your report?</p> <p>9 MR. SLATER: Didn't we go through</p> <p>10 that already --</p> <p>11 A. We already did that. I already told</p> <p>12 you that was an oversight. It's unclear the way</p> <p>13 it's written. I already told you that. I already</p> <p>14 told you that.</p> <p>15 Q. Gomm found no --</p> <p>16 A. You know, none of us are perfect.</p> <p>17 Sometimes we make mistakes.</p> <p>18 Q. I understand.</p> <p>19 A. Maybe even you do.</p> <p>20 MR. SLATER: Doctor, it's okay.</p> <p>21 Q. Gomm found no overall increased risk</p> <p>22 of cancer.</p> <p>23 Did you ever mention that fact in</p> <p>24 your report?</p> <p>25 A. No.</p>	<p style="text-align: right;">Page 288</p> <p>1 A. I don't know. I'd have to -- I have</p> <p>2 to look at it again. I'm sorry.</p> <p>3 Q. Sure.</p> <p>4 If you have to study in front of you,</p> <p>5 you might want to take a look at page 358.</p> <p>6 A. Yes. No dose-dependent effect on the</p> <p>7 risk of liver cancer was found for higher</p> <p>8 exposure, bearing lag times of six month to two</p> <p>9 years, also did not alter the effect. Valuation</p> <p>10 three year long-term use resulted in decreased</p> <p>11 sample size and showed no significant association</p> <p>12 with liver cancer. So that was 1.22, but it was</p> <p>13 not significant.</p> <p>14 So yeah, that's what they found. But</p> <p>15 I mean I really think both of these studies are</p> <p>16 somewhat flawed. That's my opinion. Because with</p> <p>17 a low-dose dimethylnitrosamine in animals, it</p> <p>18 takes time for the tumors to appear. You wouldn't</p> <p>19 get them in the same kind of time scale they're</p> <p>20 talking about here. Humans are far more</p> <p>21 susceptible to liver cancer based on exposure to</p> <p>22 dimethylnitrosamine than animals --</p> <p>23 Q. What's the --</p> <p>24 A. -- or the -- you know, the timeframe</p> <p>25 I simply think is not long enough. Even in</p>
<p style="text-align: right;">Page 287</p> <p>1 MR. SLATER: Take your time, please.</p> <p>2 A. The Gomm paper found an increased</p> <p>3 risk for liver cancer was identified, but no</p> <p>4 association was identified for the overall risk of</p> <p>5 cancer. So yeah, it's in there. It's in there.</p> <p>6 Q. All right.</p> <p>7 You've talked about what Gomm</p> <p>8 observed with respect to liver cancer.</p> <p>9 Do you understand that valsartan is a</p> <p>10 long-term-use medication?</p> <p>11 A. Yes.</p> <p>12 Q. Patients that are taking ARBs to</p> <p>13 control hypertension don't use these medications</p> <p>14 acutely, right?</p> <p>15 A. Right.</p> <p>16 Q. When they take valsartan or any ARB,</p> <p>17 the patients tend to be on them for years,</p> <p>18 correct?</p> <p>19 A. Yes.</p> <p>20 Q. In Gomm, when the authors adjusted</p> <p>21 for long-term use, isn't it true that the data</p> <p>22 could no longer find an association for liver</p> <p>23 cancer?</p> <p>24 MR. SLATER: Objection.</p> <p>25 You can answer.</p>	<p style="text-align: right;">Page 289</p> <p>1 tobacco and cancer, where you have a much stronger</p> <p>2 carcinogen, the timeframe is minimum of 20 years.</p> <p>3 Q. And that's a minimum of 20 years from</p> <p>4 exposure to the carcinogen to the development of</p> <p>5 the tumor?</p> <p>6 A. Right.</p> <p>7 Q. So, you know, anyone suggesting that</p> <p>8 they got a tumor from valsartan-containing</p> <p>9 medication that developed in a year or 18 months,</p> <p>10 that would be highly unlikely because the time</p> <p>11 period is just too short?</p> <p>12 MR. SLATER: Objection.</p> <p>13 You can answer.</p> <p>14 A. I don't know about anyone -- okay? --</p> <p>15 because, you know, there could be predisposing</p> <p>16 conditions. It could be that the person had other</p> <p>17 exposures. So I wouldn't say anyone. But in</p> <p>18 general, you would expect that the timeframe would</p> <p>19 be longer than three years.</p> <p>20 Q. You expect the timeframe to be more</p> <p>21 along the lines of ten to 15 years at least,</p> <p>22 right?</p> <p>23 A. That's what you would expect, but you</p> <p>24 know, it could be that there's something about</p> <p>25 NDMA that we don't really know about.</p>

<p style="text-align: right;">Page 290</p> <p>1 Q. It sounds like there's a lot we don't 2 know about NDMA. 3 MR. SLATER: Objection. 4 A. No, I wouldn't say that. I wouldn't 5 say that at all. We know a lot about NDMA. We 6 know a lot about it. 7 Q. Well, it sounds like you didn't hear 8 my question, so let me ask -- 9 MR. SLATER: It wasn't a question -- 10 A. There might be a co-factor involved 11 in these patients. Maybe high blood pressure or 12 hypertension previously unrecognized that shortens 13 the waiting period. 14 Q. Have you ever seen -- 15 A. No, we don't know. 16 Q. Have you ever seen a study suggesting 17 that hypertension shortens the latency period for 18 tumor development? 19 A. No, I haven't seen it. 20 Q. So we were talking about Gomm and I 21 was on page 61 and Gomm provides a table regarding 22 the authors' evaluation of single cancer outcomes. 23 Do you see that? 24 A. Yes. 25 Q. And Gomm found no statistically</p>	<p style="text-align: right;">Page 292</p> <p>1 association between lung cancer and NDMA in 2 valsartan, correct? 3 A. That's correct. But I wonder if 4 these were all nonsmokers. I don't know if that's 5 the case. 6 Q. No statistically significant 7 association between pancreatic cancer and NDMA in 8 valsartan, correct? 9 A. Correct. Well, malignant melanoma. 10 Q. No statistically significant 11 association between prostate cancer and NDMA in 12 valsartan, correct? 13 A. Correct. 14 Q. No statistically significant 15 association between uterine cancer and NDMA in 16 valsartan? 17 A. Right. 18 Q. Do you agree that the metabolism of 19 NDMA and NDEA is the only mechanism by which these 20 substances could possibly cause a mutation? 21 A. Yes. 22 Q. So NDMA and NDEA could circulate in 23 the body and unless and until they become 24 metabolized, they'll just be excreted without 25 causing harm, right?</p>
<p style="text-align: right;">Page 291</p> <p>1 significant association between bladder cancer and 2 NDMA in valsartan, right? 3 A. No. I don't see bladder cancer. 4 You're looking at table two? 5 Q. No. Table three on page -- 6 A. All right. Sorry. Yeah, right. 7 Right. They didn't -- 8 Q. Let me ask the question, please. 9 Gomm found no statistically 10 significant association between bladder cancer and 11 NDMA in valsartan, correct? 12 A. Yes, correct. 13 Q. No statistically significant 14 association between breast cancer and NDMA in 15 valsartan, correct? 16 A. Correct. 17 Q. No statistically significant 18 association between colorectal cancer and NDMA in 19 valsartan, correct? 20 A. Correct. 21 Q. No statistically significant 22 association between kidney cancer and NDMA in 23 valsartan, correct? 24 A. Correct. 25 Q. No statistically significant</p>	<p style="text-align: right;">Page 293</p> <p>1 A. Say that again, please. 2 Q. Absent -- what I was saying was until 3 NDMA and NDEA become metabolized, they would 4 simply be excreted from the body without causing 5 harm? 6 A. That's true, but, in fact, you see 7 very little excretion of unchanged NDMA in the 8 urine. When it's taken orally, it's metabolized 9 very effectively by the liver and other tissues. 10 Q. Does most of the metabolism of the 11 NDMA occur in the liver? 12 A. As far as we know, yes. 13 Q. And at this point in time, would you 14 say that the scientific community has good data on 15 the metabolism of NDMA and NDEA in the human body? 16 A. Yes. 17 Q. Do you agree then that the primary 18 metabolism of NDMA and NDEA takes place through 19 the cytochrome P450 enzyme? 20 A. Yes. 21 Q. And that's in the liver. That's 22 where that enzyme is primarily located, right? 23 A. No. They're in other tissues also. 24 Q. It's not in every organ system of the 25 body, is it?</p>

<p style="text-align: right;">Page 294</p> <p>1 A. Just about.</p> <p>2 Q. Just the enzyme?</p> <p>3 A. Yes. There are different forms in</p> <p>4 different tissues. Not just in the liver. The</p> <p>5 lung, kidney, small intestine, esophagus, oral</p> <p>6 cavity. They all have P450 enzymes. The liver,</p> <p>7 of course, is the main metabolizing organ in the</p> <p>8 body and has a higher P450 content than other</p> <p>9 tissues, but all tissues have P450s. Different</p> <p>10 ones. There are whole books written on it.</p> <p>11 Q. Okay. I'll take your word for it.</p> <p>12 Does the scientific community at this</p> <p>13 point in time have a great deal of valid reliable</p> <p>14 data about the type of DNA damage caused by NDMA</p> <p>15 and NDEA?</p> <p>16 A. Yes.</p> <p>17 Q. Have you ever stated that there are</p> <p>18 ways to look at a DNA adduct formation and how</p> <p>19 much damage comes from nitrosamine exposure but</p> <p>20 right now, in 2021, we don't have that type of</p> <p>21 data?</p> <p>22 A. I'm not sure I understand your</p> <p>23 question.</p> <p>24 Q. My question is simply have you ever</p> <p>25 made the statement that "We do not have the data</p>	<p style="text-align: right;">Page 296</p> <p>1 threshold with respect to the body's DNA repair</p> <p>2 abilities?</p> <p>3 A. May have been discussed, but I don't</p> <p>4 recall that that conclusion was made.</p> <p>5 Q. Did Dr. Guttenplan observe that the</p> <p>6 nitrosamine levels in medicines were so low that</p> <p>7 they were not approaching threshold for enzyme</p> <p>8 saturation? Do you remember that comment or</p> <p>9 observation being made?</p> <p>10 A. For which enzyme? Repair enzymes,</p> <p>11 you mean?</p> <p>12 Q. Yes, sir.</p> <p>13 A. I don't follow what you mean.</p> <p>14 Q. My question was did Dr. Guttenplan</p> <p>15 state at the FDA workshop that the levels of</p> <p>16 nitrosamines in medicines were so low that they</p> <p>17 were not approaching thresholds for enzyme</p> <p>18 saturation in the body?</p> <p>19 A. You're still not clear. First, you</p> <p>20 were talking about DNA repair enzymes and then</p> <p>21 you're talking about nitrosamine metabolizing</p> <p>22 enzymes, so I'm not sure which ones you're</p> <p>23 actually referring to.</p> <p>24 Q. When Dr. Guttenplan used the term</p> <p>25 "sub threshold," what did you understand that to</p>
<p style="text-align: right;">Page 295</p> <p>1 in 2021 to evaluate the type of DNA damage caused</p> <p>2 by nitrosamines"?</p> <p>3 A. I don't think I ever made that</p> <p>4 statement, no. We have a lot of data. We have a</p> <p>5 huge amount of data.</p> <p>6 Q. Who is Joseph Guttenplan,</p> <p>7 G-U-T-T-E-N-P-L-A-N?</p> <p>8 A. Guttenplan.</p> <p>9 Q. Sorry for the mispronunciation.</p> <p>10 Who is Joseph Guttenplan?</p> <p>11 A. He's a scientist at New York</p> <p>12 University.</p> <p>13 Q. Is he an expert in the field of</p> <p>14 chemical drug and genetic drug toxicology?</p> <p>15 A. Yes.</p> <p>16 Q. Was Dr. Guttenplan part of the FDA</p> <p>17 workshop that took place in March?</p> <p>18 A. Yes, he was there.</p> <p>19 Q. During that workshop was one of the</p> <p>20 issues that was discussed the body's DNA repair</p> <p>21 mechanisms?</p> <p>22 A. Yes.</p> <p>23 Q. In that workshop, was it discussed</p> <p>24 among the experts and agreed that the small</p> <p>25 amounts of nitrosamines in medication were sub</p>	<p style="text-align: right;">Page 297</p> <p>1 mean?</p> <p>2 A. I believe -- I believe he's talking</p> <p>3 about with respect to the nitrosamine-metabolizing</p> <p>4 enzyme, like 452E1 and others that are in the</p> <p>5 body, that those enzymes are not saturated by the</p> <p>6 kind of exposure that you would get from</p> <p>7 valsartan.</p> <p>8 Q. When those enzymes are not saturated,</p> <p>9 what that means is that our body has the ability</p> <p>10 to deal with those small levels of carcinogens,</p> <p>11 correct?</p> <p>12 A. Deal with them, yes. In dealing with</p> <p>13 them, it creates a DNA damaging agent. That</p> <p>14 metabolism is absolutely required for NDMA to</p> <p>15 cause liver cancer.</p> <p>16 Q. Who is Dr. Richard Adamson?</p> <p>17 A. He's a consultant now. He's a former</p> <p>18 director of the Division of Cancer Etiology at the</p> <p>19 National Cancer Institute, which is the US -- main</p> <p>20 US governing body that does research on cancer.</p> <p>21 Q. Was Dr. Adamson also at the workshop</p> <p>22 in March?</p> <p>23 A. Yes.</p> <p>24 Q. Do you recall Dr. Adamson also</p> <p>25 discussing the issue of the body's DNA repair</p>

<p style="text-align: right;">Page 298</p> <p>1 mechanisms and whether low levels of NDMA or NDEA 2 in drug products was expected to present a 3 significant risk of harm to the patient 4 population? 5 A. I don't recall his exact comments, 6 but he's certainly an expert. He has done studies 7 exposing primates to NDEA. 8 Q. Isn't it true that Dr. Adamson stated 9 that the low levels of nitrosamines in the drugs 10 were so low that he would not expect any long-term 11 risk of patient health since there was no 12 saturation or competition for activation of the 13 body's repair enzymes at those levels? 14 A. Are you quoting? 15 Q. I'm asking if that's what you heard 16 him say. 17 A. I don't remember if that's what I 18 heard him say. I'm asking you whether you're 19 quoting from the transcript. In that case, it's 20 true. 21 Q. So is that statement correct, that 22 low levels of exposure to nitrosamines would not 23 be expected to cause long-term harm to the patient 24 population because those levels would not be 25 expected to saturate or compete for activation of</p>	<p style="text-align: right;">Page 300</p> <p>1 in March, was it the conclusion of the scholars 2 that were impaneled by FDA that the levels in this 3 case were so low that there was not expected to be 4 a significant risk to public health because the 5 body's repair mechanisms would allow for or 6 prevent the development of mutations? 7 A. Yes, that was the conclusion. 8 Q. I guess -- 9 MR. SLATER: Objection. 10 A. What? 11 Q. I guess then what I'd like to ask you 12 is this -- 13 A. Are you quoting? I mean, were you 14 quoting from the report? 15 MR. SLATER: Doctor, if you want to 16 see the transcripts, you could ask him to 17 show it to you. 18 Q. I'm just asking you a question. 19 A. I'm just asking you whether you're 20 quoting from the report or not. 21 Q. I asked you if that was a conclusion 22 of the panelists. 23 A. I don't remember. I mean, you have 24 the report right in front of you, so why don't you 25 tell me?</p>
<p style="text-align: right;">Page 299</p> <p>1 the body's repair enzymes? 2 MR. SLATER: Objection. 3 Lack of foundation. Multiple -- 4 A. It's totally confusing, what you're 5 saying. Okay? The low levels would be very 6 effectively metabolized by the P450s in the liver 7 and other tissues of the body, leading to the 8 formation of highly reactive DNA damaging 9 intermediates that cause mutations in DNA. Some 10 of those may be repaired by a repair enzyme such 11 as MGMT and I think what you're saying is that the 12 MGMT activity would not be saturated. I think 13 that's what you're referring to, but the way 14 you're saying is it very confusing. Really 15 muddies the water. 16 The bottom line is that your body 17 definitely has the ability to convert the NDMA in 18 valsartan to a DNA methylating agent that's going 19 to form O6-methylguanine. I can tell you with 20 100% certainty that a person who takes a tablet of 21 valsartan that's contaminated with 22 dimethylnitrosamine will form a finite amount of 23 O6-methylguanine in their DNA. Some of that may 24 be repaired. Some of it may lead to mutations. 25 Q. My question was at the FDA workshop</p>	<p style="text-align: right;">Page 301</p> <p>1 Q. We know that you've done research on 2 NNN and NNK in your career and we know that both 3 of those are known Class 1 carcinogens in tobacco, 4 right? 5 A. Correct. 6 Q. We know that tobacco also is laced 7 with other carcinogens, not just those two tobacco 8 nitrosamines, right? 9 A. Tobacco smoked, yes. Unburnt tobacco 10 is another story. 11 Q. I've been led to believe -- and I 12 don't know whether it's true or not -- is that 13 tobacco contained over 70 carcinogens. 14 Is that the case? 15 A. Tobacco smoke, yes. 16 Q. I think that you have written that 17 cigarette smoking causes up to 90% of all the lung 18 cancers in the world and is the largest cause of 19 cancer death in the world, yet only ten to 20% of 20 lifetime smokers will get lung cancer? 21 A. Correct. It's no longer the largest 22 cause of cancer in women in the world. That's 23 breast cancer. But everything else you said is 24 correct. 25 Q. All right.</p>

<p style="text-align: right;">Page 302</p> <p>1 We talked earlier about the Gushgari</p> <p>2 paper that told us that the estimate is that</p> <p>3 smoking leads to the injection of 25,000 nanograms</p> <p>4 of nitrosamines per day.</p> <p>5 Do you remember that?</p> <p>6 A. Yes.</p> <p>7 Q. And I assume that doesn't need --</p> <p>8 that's not even taking into account then the other</p> <p>9 carcinogens contained in tobacco smoke, right?</p> <p>10 A. Correct.</p> <p>11 Q. So if only ten to 20% of individuals</p> <p>12 exposed to 25,000 nanograms a day of nitrosamines</p> <p>13 plus other carcinogens acquire lung cancer after a</p> <p>14 lifetime of smoking, do you have any estimate or</p> <p>15 are you capable of providing an estimate as to the</p> <p>16 percentage of valsartan users that you would</p> <p>17 expect to develop cancer from a less-than-lifetime</p> <p>18 exposure to nitrosamines?</p> <p>19 A. I'm not capable of making that</p> <p>20 calculation, but presumably the risk would be less</p> <p>21 than from smoking.</p> <p>22 Q. Do you know what the --</p> <p>23 A. I cannot make that calculation.</p> <p>24 Q. Okay. Fair enough.</p> <p>25 Do you know what the background rate</p>	<p style="text-align: right;">Page 304</p> <p>1 A. Definitely available.</p> <p>2 Q. I understand. I'm only asking --</p> <p>3 A. I can't keep all those figures in my</p> <p>4 brain.</p> <p>5 Q. I'm just asking what you know. If</p> <p>6 you don't know, just tell me you don't know.</p> <p>7 Do you intend to present this court</p> <p>8 with any statistical or epidemiological evidence</p> <p>9 to say that there will be a statistically</p> <p>10 significant increased rate of cancer above the</p> <p>11 background rate simply because of a</p> <p>12 less-than-lifetime increase in the intake of NDMA</p> <p>13 when all of the individual plaintiffs have already</p> <p>14 been exposed to nitrosamines exogenously every day</p> <p>15 of their life?</p> <p>16 MR. SLATER: Objection.</p> <p>17 You can answer.</p> <p>18 A. First of all, your question doesn't</p> <p>19 make a lot of sense the way --</p> <p>20 Q. Well, which part doesn't --</p> <p>21 A. The way that all the people have been</p> <p>22 exposed to nitrosamines every day of their life.</p> <p>23 That's incredibly nonquantitative. I mean, I</p> <p>24 could never agree with a statement like that.</p> <p>25 In any case, I'm not intending to</p>
<p style="text-align: right;">Page 303</p> <p>1 of cancer in the US population is?</p> <p>2 A. What do you mean by background rate?</p> <p>3 Q. How many people will get cancer in</p> <p>4 one form or another in their lifetime?</p> <p>5 A. Yes. I know that number, but I'm</p> <p>6 afraid I can't quote it off the top of my head.</p> <p>7 But that number is certainly available.</p> <p>8 Q. Okay.</p> <p>9 Do you know what the background rate</p> <p>10 of cancer among Americans over the age of 50 who</p> <p>11 suffer from hypertension might be?</p> <p>12 A. Not offhand.</p> <p>13 Q. Are you able --</p> <p>14 A. I don't know what you mean by</p> <p>15 background.</p> <p>16 Q. Maybe --</p> <p>17 A. What does background mean?</p> <p>18 Q. Maybe it's just my poor language.</p> <p>19 I'm just trying to tell, you know,</p> <p>20 how many -- what percentage of Americans over the</p> <p>21 age of 50 who have hypertension will develop</p> <p>22 cancer?</p> <p>23 A. I can't answer that offhand. It's</p> <p>24 definitely available.</p> <p>25 Q. I'm only asking --</p>	<p style="text-align: right;">Page 305</p> <p>1 make any numerical estimates because that's not</p> <p>2 what I do. That's for the risk assessors to do.</p> <p>3 Q. That's fine. This is what I'm just</p> <p>4 trying to find out. Let's just assume</p> <p>5 hypothetically that those readily-available</p> <p>6 statistics you talk about tell us that 30% of</p> <p>7 people over the age of 50 who have hypertension</p> <p>8 will develop cancer in one form or another.</p> <p>9 Okay?</p> <p>10 A. Okay.</p> <p>11 Q. And you just accept that number --</p> <p>12 A. Okay.</p> <p>13 Q. -- for the purpose of my question.</p> <p>14 A. Right.</p> <p>15 Q. What I'm trying to figure out is are</p> <p>16 you going to offer an opinion that that population</p> <p>17 subgroup is at some statistical increased risk of</p> <p>18 cancer just because they received a</p> <p>19 less-than-lifetime increase in the intake of NDEA</p> <p>20 or NDMA for some period of time?</p> <p>21 A. Yes. I would be comfortable with</p> <p>22 offering an opinion, but not necessarily making a</p> <p>23 calculation.</p> <p>24 Q. Well, that was my question.</p> <p>25 What is the -- what is that increased</p>

<p style="text-align: right;">Page 306</p> <p>1 risk? Can you calculate it or estimate it?</p> <p>2 A. No, I can't. I can't do that.</p> <p>3 That's not what I do.</p> <p>4 Q. That would be the same thing for -- I</p> <p>5 think I --</p> <p>6 A. For both.</p> <p>7 Q. That would be the case for both</p> <p>8 NDMA and NDEA --</p> <p>9 A. That's for the risk assessor to do.</p> <p>10 Like EMA and any others.</p> <p>11 MR. TRISCHLER: I think I'm ready to</p> <p>12 pass the witness.</p> <p>13 I think the information that I</p> <p>14 received, Adam, is that there are others who</p> <p>15 have -- a few others that have questions,</p> <p>16 maybe one or two on the side, but I'll let</p> <p>17 them speak for themselves and I don't know if</p> <p>18 that's been updated since I finished. So --</p> <p>19 but I think --</p> <p>20 MR. SLATER: Whoever it is needs to</p> <p>21 identify themselves and I'm going to object</p> <p>22 to and expect that there will not be any</p> <p>23 questioning that's going to go into the areas</p> <p>24 that Mr. Trischler covered.</p> <p>25 It's hard for me to imagine there is</p>	<p style="text-align: right;">Page 308</p> <p>1 been a thorough deposition and we should be</p> <p>2 able to turn it over to me soon.</p> <p>3 So go ahead. Start asking your</p> <p>4 questions, please.</p> <p>5 MR. FOWLER: I will and I'll</p> <p>6 appreciate if you simply just object to</p> <p>7 form and --</p> <p>8 MR. SLATER: I don't need a</p> <p>9 coaching --</p> <p>10 MR. FOWLER: -- launching into the</p> <p>11 diatribes I've been hearing all day, so just</p> <p>12 object to form and I'll ask my questions.</p> <p>13 MR. SLATER: Okay. Now that you</p> <p>14 you're done talking I'll respond.</p> <p>15 Please don't coach me. Please don't</p> <p>16 tell me what to do --</p> <p>17 MR. FOWLER: Same here.</p> <p>18 MR. SLATER: -- but please realize</p> <p>19 that duplicative questions, you'll need to</p> <p>20 move from question to question.</p> <p>21 You may proceed.</p> <p>22 MR. FOWLER: What I'd like to do</p> <p>23 first -- good afternoon, Dr. Hecht. My name</p> <p>24 is Steve Fowler on behalf of the Teva</p> <p>25 defendants.</p>
<p style="text-align: right;">Page 307</p> <p>1 anything new to ask, but please don't come in</p> <p>2 and make me start objecting and have a back</p> <p>3 and forth. I would appreciate that because</p> <p>4 it's been a long day and I have some</p> <p>5 questions to follow up on from Mr.</p> <p>6 Trischler's lengthy questioning.</p> <p>7 MR. FOWLER: Good afternoon,</p> <p>8 Dr. Hecht. It's Steven Fowler with Greenberg</p> <p>9 Traurig.</p> <p>10 I believe the remaining defendants</p> <p>11 have an hour and a half or so of questions.</p> <p>12 I've got quite a bit of questions. I assure</p> <p>13 you it's not my intent to ask any questions</p> <p>14 that Dr. Hecht has answered, but I do have</p> <p>15 questions and I'm just -- in fairness, I</p> <p>16 think it's about an hour and a half or so --</p> <p>17 MR. SLATER: Go ahead. Start your</p> <p>18 questioning. I've heard that before.</p> <p>19 Let's get going and we'll go question</p> <p>20 by question and see if it's new questions</p> <p>21 because it's impossible for me to imagine --</p> <p>22 unless you guys are just going to walk the</p> <p>23 dog and come up with things to ask about that</p> <p>24 are hyper specific to a specific manufacturer</p> <p>25 just to ask questions, I feel like this has</p>	<p style="text-align: right;">Page 309</p> <p>1 What I'd like to do first is actually</p> <p>2 mark as the next exhibit your Notice of</p> <p>3 Deposition today. I don't think that that's</p> <p>4 been marked.</p> <p>5 Can we get that marked --</p> <p>6 MR. SLATER: You're going to need to</p> <p>7 do that yourself, sir. You're going to</p> <p>8 have to have someone put it up.</p> <p>9 MR. FOWLER: Adam, I'm not talking to</p> <p>10 you.</p> <p>11 Steve, are you able to share the</p> <p>12 screen? We have three Steves on the line.</p> <p>13 THE VIDEOGRAPHER: Do you have</p> <p>14 somebody else who is going to be displaying?</p> <p>15 MR. FOWLER: The exhibit was just</p> <p>16 introduced and it can be displayed by the</p> <p>17 concierge as I understand.</p> <p>18 THE VIDEOGRAPHER: As far as the</p> <p>19 record, it will be Exhibit 23.</p> <p>20 (Whereupon, Exhibit 23 was marked for</p> <p>21 identification.)</p> <p>22 MR. FOWLER: Is it going to be</p> <p>23 displayed or am I going to --</p> <p>24 MR. SLATER: It's on the screen.</p> <p>25</p>

<p style="text-align: right;">Page 310</p> <p>1 EXAMINATION BY</p> <p>2 MR. FOWLER:</p> <p>3 Q. Doctor, have you seen this document</p> <p>4 before?</p> <p>5 A. No.</p> <p>6 Q. I would submit this is the notice for</p> <p>7 you today and if we can go to page three of the</p> <p>8 notice, you'll see that we've asked for certain</p> <p>9 items to be brought with you and that would</p> <p>10 include any sort of files or records that you have</p> <p>11 with regard to this subject matter.</p> <p>12 And Dr. Hecht, I heard today you've</p> <p>13 spent much of your career on nitrosamines and my</p> <p>14 question to you is do you have a file that you've</p> <p>15 maintained on nitrosamines and the risk of</p> <p>16 carcinogenicity?</p> <p>17 A. A file on risk of carcinogenicity in</p> <p>18 humans? In animals?</p> <p>19 Q. Let me break it down.</p> <p>20 Do you have a file on nitrosamines,</p> <p>21 Doctor?</p> <p>22 A. A file? Everything is summarized in</p> <p>23 my publications. I mean, I do not have all of the</p> <p>24 original records from the research that we've</p> <p>25 done. I have files and --</p>	<p style="text-align: right;">Page 312</p> <p>1 have binders? What do you have, sir?</p> <p>2 A. In my office?</p> <p>3 MR. SLATER: Dr. Hecht, one second.</p> <p>4 This was covered extensively earlier.</p> <p>5 MR. FOWLER: It wasn't. I've seen</p> <p>6 him picking up things and looking at things.</p> <p>7 I just want to know what else he's got.</p> <p>8 THE WITNESS: You want me to answer</p> <p>9 him?</p> <p>10 MR. SLATER: Yeah, go ahead, answer</p> <p>11 him.</p> <p>12 We've moving quickly towards</p> <p>13 concluding his questioning if this is --</p> <p>14 A. I have binders that have the</p> <p>15 publications and the other data that was mentioned</p> <p>16 in the written document and I have some of my</p> <p>17 books that I refer to, including, you know, the</p> <p>18 IARC 1978 valuation. I have all of the IARC</p> <p>19 monographs up until about year 2000 or maybe a</p> <p>20 little later. They're not all here in my office</p> <p>21 anyhow.</p> <p>22 Q. Thank you, sir.</p> <p>23 A. Does that answer your question?</p> <p>24 Q. I believe so, sir. Thank you.</p> <p>25 Doctor, when evaluating the issue</p>
<p style="text-align: right;">Page 311</p> <p>1 Q. Do you maintain any -- setting aside</p> <p>2 this litigation, Doctor, do you maintain a file on</p> <p>3 nitrosamine as being an area of your research</p> <p>4 we've heard about today?</p> <p>5 A. Yes, I do. Yes.</p> <p>6 Q. And do you maintain that with paper</p> <p>7 copies of journal articles you may have printed</p> <p>8 over the years?</p> <p>9 A. Yes. I have several file cabinets,</p> <p>10 but, you know, in the last, I don't know, eight</p> <p>11 years or so, everything is online.</p> <p>12 Q. Is your file on nitrosamines</p> <p>13 organized at all by particular nitrosamines such</p> <p>14 as NDMA or NDEA?</p> <p>15 A. No.</p> <p>16 Q. When you were asked to participate in</p> <p>17 the FDA panel, did you undertake any preparation</p> <p>18 for that panel? Did you undertake any research</p> <p>19 before you appeared?</p> <p>20 A. No.</p> <p>21 Q. With you today, Doctor, do you have</p> <p>22 any -- let me ask you this: I've seen you pick up</p> <p>23 the red book a couple times.</p> <p>24 What else do you have in your space</p> <p>25 there at your office? Can you hold it up? Do you</p>	<p style="text-align: right;">Page 313</p> <p>1 before you, which I think we've acknowledged is</p> <p>2 whether the level of NDMA and NDEA found in the</p> <p>3 valsartan products increases the risk of</p> <p>4 carcinogenicity, did you apply a specific level</p> <p>5 of -- let's start with NDMA -- in your analysis as</p> <p>6 it pertains to the valsartan products?</p> <p>7 MR. SLATER: Objection.</p> <p>8 You can answer.</p> <p>9 A. No. I mean, I did not do a risk</p> <p>10 assessment.</p> <p>11 Q. Am I correct you were --</p> <p>12 A. That was done by others.</p> <p>13 Q. You were attempting to evaluate</p> <p>14 whether or not the levels of NDMA and NDEA in the</p> <p>15 valsartan tablets poses an increased risk. Wasn't</p> <p>16 that what the question you were answering? I</p> <p>17 thought we heard that earlier.</p> <p>18 MR. SLATER: Objection.</p> <p>19 Asked and answered.</p> <p>20 You can answer.</p> <p>21 A. I don't know what you mean by</p> <p>22 increased risk. Sure, there's an increase in</p> <p>23 risk. No doubt about it. It shouldn't be there.</p> <p>24 The amount should be zero, but I didn't -- I did</p> <p>25 not do the formal risk assessment. Those were</p>

<p style="text-align: right;">Page 314</p> <p>1 done by FDA and EMA, among others.</p> <p>2 Q. What level --</p> <p>3 A. And I don't do it. That's not what I</p> <p>4 do.</p> <p>5 Q. I understand, Doctor.</p> <p>6 What level of NDMA are you operating</p> <p>7 from when evaluating the valsartan?</p> <p>8 A. Zero.</p> <p>9 Q. Doctor, you understand FDA has</p> <p>10 found --</p> <p>11 A. It should be zero.</p> <p>12 Q. Doctor, that's a liability --</p> <p>13 A. It should be zero.</p> <p>14 Q. This can take a while.</p> <p>15 A. The amounts that have been found in</p> <p>16 the API from ZHP ranged from about ten to 120</p> <p>17 parts per million, I believe.</p> <p>18 Q. Do you believe that the levels in the</p> <p>19 API is the same as the levels of NDMA in finished</p> <p>20 dose valsartan products?</p> <p>21 A. No. No. It would be -- it would be</p> <p>22 higher than the API for finished products.</p> <p>23 Q. Right.</p> <p>24 So we're only here today about the</p> <p>25 finished dose products that plaintiffs allegedly</p>	<p style="text-align: right;">Page 316</p> <p>1 You may proceed.</p> <p>2 Q. Doctor, what I was trying to get at</p> <p>3 earlier is simply this question: Do you think and</p> <p>4 agree that it's reasonable for those scientists</p> <p>5 who are evaluating the risk, if any, from the</p> <p>6 levels of NDMA and NDEA in the valsartan to use</p> <p>7 the geometric mean value of all of the levels FDA</p> <p>8 measured in a particular dose of valsartan?</p> <p>9 MR. SLATER: Objection.</p> <p>10 I don't understand.</p> <p>11 THE WITNESS: Do you want me to</p> <p>12 answer that now?</p> <p>13 MR. SLATER: If you can --</p> <p>14 A. Were you going to reply to his</p> <p>15 objection first?</p> <p>16 Q. I have no reason to.</p> <p>17 Go ahead, Doctor, if you do</p> <p>18 understand the question.</p> <p>19 A. Could you repeat it again please?</p> <p>20 Q. Yes, sir.</p> <p>21 Do you agree it makes sense to take</p> <p>22 an average number, a geometric mean of all of the</p> <p>23 various manufacturers levels of NDMA measured by</p> <p>24 FDA in, let's say, the 320 milligram dose of</p> <p>25 valsartan when evaluating what, if any, risk</p>
<p style="text-align: right;">Page 315</p> <p>1 consumed and my question is simply this --</p> <p>2 MR. SLATER: You know what, counsel?</p> <p>3 Before you ask a question, we're taking a</p> <p>4 break.</p> <p>5 MR. FOWLER: Don't talk over me.</p> <p>6 MR. SLATER: We're taking a break.</p> <p>7 We've been going over an hour again. It's</p> <p>8 5:30 on the east coast, it's 4:30 -- the</p> <p>9 doctor has been going for now</p> <p>10 eight-and-a-half hours, so we're going to</p> <p>11 take a break.</p> <p>12 MR. FOWLER: I was in the middle of a</p> <p>13 question --</p> <p>14 MR. SLATER: I stopped you before you</p> <p>15 asked it, you talked over me. We're going to</p> <p>16 take a break for ten minutes.</p> <p>17 MR. FOWLER: Okay.</p> <p>18 Thank you, Doctor. We will take a</p> <p>19 break.</p> <p>20 THE VIDEOGRAPHER: Time is 5:34.</p> <p>21 This concludes media five.</p> <p>22 (Recess taken)</p> <p>23 THE VIDEOGRAPHER: The time is now</p> <p>24 5:49.</p> <p>25 This begins media six.</p>	<p style="text-align: right;">Page 317</p> <p>1 exists from that level of NDMA?</p> <p>2 Do you understand that?</p> <p>3 A. Yeah. You want to take the geometric</p> <p>4 mean from all of the manufacturers. I'm not sure</p> <p>5 that really makes sense because the different</p> <p>6 manufacturers may have different amounts.</p> <p>7 Q. For example, you would not expect any</p> <p>8 single patient to have taken the highest level of</p> <p>9 NDMA detected in the 320 milligram valsartan for</p> <p>10 the period at issue, would you?</p> <p>11 MR. SLATER: Objection.</p> <p>12 A. I wouldn't know. I have no idea.</p> <p>13 Q. So do you think it's unreasonable to</p> <p>14 take an average number of all of the manufacturers</p> <p>15 of the affected valsartan when evaluating the</p> <p>16 risk?</p> <p>17 MR. SLATER: Objection.</p> <p>18 You can answer again.</p> <p>19 A. I really don't know. I mean, an</p> <p>20 average would be the place to start, I suppose.</p> <p>21 Q. Okay.</p> <p>22 A. You know, one would have to be</p> <p>23 mindful also of the high doses because the high</p> <p>24 doses are where you more likely see an effect. So</p> <p>25 it might make sense to evaluate the high doses</p>

<p style="text-align: right;">Page 318</p> <p>1 first, you know, above, let's say, the 80th 2 percentile, something like that. And you know, if 3 you didn't find an effect there, then you could 4 probably safely conclude that there would be no 5 effect to the lower doses. 6 So I'm not sure that the geometric 7 mean is necessarily the way to go about this. As 8 I mentioned, I'm not the risk assessor, so you 9 really -- you're bringing me into an area that's 10 not my area of expertise. 11 Q. Yes, sir, thank you. 12 And it follows from that that you 13 made no attempt to evaluate the specific level of 14 NDMA from any of the manufacturers' valsartan 15 tablets that FDA measured. You didn't consider 16 any of those specific levels in forming the 17 opinions we see in your report; is that correct? 18 MR. SLATER: Objection. 19 A. I didn't do calculations, no. 20 Q. You didn't rely on any of the 21 specific numbers that FDA measured in any of the 22 valsartan in forming the opinions contained in 23 your report, correct? 24 MR. SLATER: Objection. 25 Lack of foundation.</p>	<p style="text-align: right;">Page 320</p> <p>1 Do you agree with that? 2 A. Yes. 3 Q. Doctor, forgive me, I'm going to -- 4 in an effort to be efficient, I'm going to jump 5 around a little bit, so forgive me if they're 6 disjointed and if you don't follow me, please let 7 me know. 8 Exhibit 1 is your report. If you 9 could please -- I'll direct your attention to page 10 eight. 11 A. Okay. 12 Q. The last full paragraph that begins 13 "The pharmacokinetics ..." -- are you with me, 14 sir? 15 A. Yes. 16 Q. You state in the third line 17 "Consistently, these studies have demonstrated 18 high systemic clearance and high oral 19 bioavailability of NDMA." 20 Do you see that? 21 A. Yes. 22 Q. The support for that statement is 23 contained in part of that Dr. Gombar beagle study 24 that we looked at; is that correct? 25 A. Yeah.</p>
<p style="text-align: right;">Page 319</p> <p>1 You can answer. 2 A. Come back to it again. I mean, I 3 didn't do a formal risk assessment. That's not 4 what I do. So -- 5 Q. I understand, Doctor. 6 A. -- I don't really know what you're 7 driving at with this question. I already told you 8 I don't do these calculations. EMA did 9 calculations, FDA did calculations. Their results 10 are, I think, all documented. 11 Q. In your research -- 12 A. I don't really see what you're 13 asking -- why you're asking me. I mean, ask the 14 person at EMA who did the calculations. 15 Q. Thank you, Doctor. 16 When you've done your research on 17 other nitrosamines and in tobacco, like the NNN 18 and NNK, do you ever evaluate the level of NNN or 19 NNK in writing your papers or forming your 20 conclusions on those studies? 21 A. Yes, we do. 22 Q. The levels are important, correct? 23 A. Yes, they are. 24 Q. I think we started the day with dose 25 and duration are a key to any evaluation.</p>	<p style="text-align: right;">Page 321</p> <p>1 Q. And if we could please look again at 2 Exhibit -- at Exhibit 8, the beagle study -- 3 THE VIDEOGRAPHER: Would you like 4 that up on the screen, Counsel? 5 MR. FOWLER: Just pause on that. 6 I may be able to move quicker. 7 Q. Doctor, let me ask you do you have 8 any understanding of the -- any differences 9 between the metabolism of the capacity of a beagle 10 to metabolize NDMA with the CYP2E1 enzyme compared 11 to humans? Do you have any understanding of that? 12 A. I don't know if 2E1 has actually been 13 identified in beagles. I'm not sure of that. 14 Q. If beagles -- 15 A. I think Gombar's conclusions were 16 actually a little bit different. I think, if I 17 remember correctly, the beagle studies came to a 18 slightly different conclusion regarding the 19 clearance of NDMA by the liver than the other 20 studies. 21 Q. Doctor, if a beagle only has a 22 quarter of the metabolic capacity for NDMA as 23 compared to a human, would you agree that dogs 24 would have less capacity to clear any oral dose of 25 NDMA?</p>

<p style="text-align: right;">Page 322</p> <p>1 A. Sure. I mean, if they have less --</p> <p>2 if they have -- if they have less of the P450</p> <p>3 metabolizing enzymes in their liver and other</p> <p>4 tissue than humans, then they would have less</p> <p>5 capacity to clear the dose of the metabolism.</p> <p>6 Q. Do you recall the manner of exposure</p> <p>7 in that beagle study? Do you recall whether it</p> <p>8 was by IV?</p> <p>9 A. I think it was IV.</p> <p>10 Q. And you agree, Doctor, with regard to</p> <p>11 metabolism, the route of exposure is essential to</p> <p>12 understanding the route of metabolism, correct?</p> <p>13 A. Right.</p> <p>14 Q. And the route of exposure makes a</p> <p>15 difference in the route of metabolism; true?</p> <p>16 A. It can effect it, sure.</p> <p>17 Q. So the metabolism that you would</p> <p>18 expect from an IV or an IP administration of a</p> <p>19 compound like NDMA, you would expect that to show</p> <p>20 different results than through an ingestion of an</p> <p>21 oral tablet containing some level of NDMA,</p> <p>22 correct?</p> <p>23 A. Possibly.</p> <p>24 Q. That's a medical fact, isn't it,</p> <p>25 Doctor, that if it's injected IP, it's not going</p>	<p style="text-align: right;">Page 324</p> <p>1 Correct, Dr. Hecht?</p> <p>2 A. Say it again.</p> <p>3 Q. There's a third article in Dr.</p> <p>4 Gombar's series, if you will, on the</p> <p>5 pharmacokinetics of N-nitrosodimethylamine.</p> <p>6 Right?</p> <p>7 A. Okay.</p> <p>8 MR. FOWLER: I'd like to mark the</p> <p>9 next exhibit.</p> <p>10 This is the Gombar article, 1990,</p> <p>11 "Interspecies scaling of pharmacokinetics of</p> <p>12 then nitrosodimethylamine."</p> <p>13 Bear with me, Doctor.</p> <p>14 That should pop up.</p> <p>15 THE VIDEOGRAPHER: I'm looking for</p> <p>16 it. You didn't upload it by any chance, did</p> <p>17 you?</p> <p>18 MR. FOWLER: I just uploaded it as</p> <p>19 Exhibit 24.</p> <p>20 THE VIDEOGRAPHER: Excellent. Give</p> <p>21 me one moment to download it. I'm not seeing</p> <p>22 it on our Novak share file.</p> <p>23 Did you put it on the Veritext</p> <p>24 Exhibit Share by any chance?</p> <p>25 MR. FOWLER: Yes.</p>
<p style="text-align: right;">Page 323</p> <p>1 to enter the liver through the mesentery vessels,</p> <p>2 is it?</p> <p>3 A. Well, the distribution will be</p> <p>4 different, but ultimately, it'll be metabolized.</p> <p>5 Q. Would it be metabolized -- it would</p> <p>6 reach organs that orally ingested via a tablet</p> <p>7 would never reach, correct, Doctor?</p> <p>8 A. I don't know about never, but ...</p> <p>9 Q. Okay.</p> <p>10 Are you intending to offer an opinion</p> <p>11 as kind of set forth on Exhibit 8 that in humans</p> <p>12 that NDMA has a high systemic clearance and high</p> <p>13 oral bioavailability?</p> <p>14 A. That's what the literature indicates.</p> <p>15 Q. Is there any literature other than</p> <p>16 the Gombar articles on pharmacokinetics that</p> <p>17 you're relying on, sir?</p> <p>18 A. It's been done in multiple different</p> <p>19 species pharmacokinetic studies. There's a lot of</p> <p>20 them. There's a lot of data --</p> <p>21 Q. Yes, sir.</p> <p>22 A. -- as stated in the report.</p> <p>23 Q. There was a third article in the</p> <p>24 Gombar series of pharmacokinetic testing that you</p> <p>25 had in your materials.</p>	<p style="text-align: right;">Page 325</p> <p>1 (Whereupon, Exhibit 24 was marked for</p> <p>2 identification.)</p> <p>3 Q. Doctor, do you happen to have a hard</p> <p>4 copy of this in your materials?</p> <p>5 A. No.</p> <p>6 Q. We'll do it on the screen. That's</p> <p>7 fine, sir. Okay. Thank you.</p> <p>8 If we can please turn to the third</p> <p>9 page where it begins the discussion -- it's</p> <p>10 article page 4368. There you go.</p> <p>11 The very first sentence of that</p> <p>12 discussion, sir, states "The role that the</p> <p>13 pharmacokinetics of a carcinogen plays its impact,</p> <p>14 both qualitatively, i.e. target organ, and</p> <p>15 quantitatively, i.e. risk assessment, has not been</p> <p>16 adequately determined for most compounds assumed</p> <p>17 or suspected to be human carcinogens."</p> <p>18 Did I read that correctly there,</p> <p>19 Doctor?</p> <p>20 A. Yes.</p> <p>21 Q. Do you agree that for NDMA and NDEA</p> <p>22 there has been sufficient study done to adequately</p> <p>23 understand the metabolism of those two</p> <p>24 nitrosamines?</p> <p>25 A. There's pretty extensive data, yes.</p>

<p style="text-align: right;">Page 326</p> <p>1 Q. Yes, sir.</p> <p>2 A. I agree that it's pretty well</p> <p>3 understood.</p> <p>4 Q. Okay.</p> <p>5 A. There's always questions remaining.</p> <p>6 Q. You'll see at the bottom of that that</p> <p>7 it says "The root of administration can alter the</p> <p>8 organospecificity as can" -- and it flips to the</p> <p>9 next page -- "as can manipulation of the clearance</p> <p>10 with inducers or inhibitors of metabolism."</p> <p>11 Do you see that, sir?</p> <p>12 A. Yes.</p> <p>13 Q. So do you agree with that, that the</p> <p>14 route of administration can affect the</p> <p>15 organospecificity of where perhaps NDMA may land?</p> <p>16 A. I agree with it, but if I'm not</p> <p>17 mistaken, most studies of NDMA in animals</p> <p>18 carcinogenicity studies independent of the root of</p> <p>19 administration show mainly liver cancer.</p> <p>20 Q. Doctor, did you evaluate the animal</p> <p>21 studies with an eye towards the route of</p> <p>22 administration to assess those which best can be</p> <p>23 analogized to the oral administration through a</p> <p>24 tablet? Did you make that --</p> <p>25 A. No, not specifically, but I know</p>	<p style="text-align: right;">Page 328</p> <p>1 Are you aware of any study that</p> <p>2 demonstrates at low doses that NDMA has caused any</p> <p>3 downstream cancer from the liver?</p> <p>4 MR. SLATER: Objection.</p> <p>5 You can answer.</p> <p>6 A. Sure. It causes kidney cancer when</p> <p>7 the doses exceed a certain level that aren't</p> <p>8 metabolized by the liver when it's given orally,</p> <p>9 the doses are too high -- or not too high -- but</p> <p>10 higher doses will get kidney cancer.</p> <p>11 Q. Yes, Doctor.</p> <p>12 Do you agree that NDMA and NDEA are</p> <p>13 subject to first pass metabolism?</p> <p>14 A. Yes.</p> <p>15 Q. Have you made any attempt to</p> <p>16 determine what the saturation level is for the</p> <p>17 liver's capacity to handle first pass metabolism</p> <p>18 NDMA?</p> <p>19 Do you understand that question?</p> <p>20 A. In what species?</p> <p>21 Q. Human, sir.</p> <p>22 A. Have I made any attempt? No.</p> <p>23 Q. Have you made any attempt using any</p> <p>24 of the animal data to understand at what level the</p> <p>25 liver's ability to fully metabolize and excrete</p>
<p style="text-align: right;">Page 327</p> <p>1 generally in the literature that the main target</p> <p>2 tissue of NDMA in animals -- laboratory animals --</p> <p>3 is the liver and it's not all by oral</p> <p>4 administration.</p> <p>5 Q. Doctor, if I use the term "downstream</p> <p>6 organs" --</p> <p>7 A. But there are exceptions.</p> <p>8 Q. Thank you. I'm sorry. I didn't mean</p> <p>9 to step on your response.</p> <p>10 If I use the term "downstream organs</p> <p>11 to deliver," do you understand what I mean?</p> <p>12 A. Yes.</p> <p>13 Q. Okay.</p> <p>14 Are you aware of any study that was</p> <p>15 performed on animals using oral ingestion via a</p> <p>16 tablet -- not drinking water -- via oral ingestion</p> <p>17 that demonstrated any cancers outside the liver in</p> <p>18 any oral ingestion studies?</p> <p>19 A. Of a tablet?</p> <p>20 Q. Or they have -- and I can't remember</p> <p>21 the name of the tool where they just put it right</p> <p>22 down the gullet, but not drinking water is my</p> <p>23 point, Doctor.</p> <p>24 A. Yes. Oral intubation.</p> <p>25 Q. Thank you, sir.</p>	<p style="text-align: right;">Page 329</p> <p>1 the NDMA is exceeded?</p> <p>2 A. That data is in the literature.</p> <p>3 There's plenty of data on that --</p> <p>4 Q. Did you make any --</p> <p>5 A. -- from the pharmacokinetic studies</p> <p>6 and even from the early studies of Magee and Swan</p> <p>7 that when the metabolic capacity of the liver is</p> <p>8 exceeded in an oral dose, then kidney tumors start</p> <p>9 to appear and there's plenty of data on that. Not</p> <p>10 only tumors, but DNA adduct studies and metabolism</p> <p>11 studies. There's a lot of data regarding the</p> <p>12 first pass clearance of NDMA given orally, a lot</p> <p>13 of data. We understand that really very well.</p> <p>14 Q. So it follows, Doctor, that you would</p> <p>15 understand and agree with the point that NDMA will</p> <p>16 not escape the liver unless the level is at such a</p> <p>17 point that it exceeds the liver's capacity to</p> <p>18 metabolize it, correct?</p> <p>19 A. That's what the -- that's what all</p> <p>20 the data indicates. That's correct.</p> <p>21 Q. I'm also correct that sitting here</p> <p>22 today, you are offering no opinion as to what that</p> <p>23 level of NDMA is, correct?</p> <p>24 A. In humans?</p> <p>25 Q. Sir, yes.</p>

<p style="text-align: right;">Page 330</p> <p>1 A. I'm not.</p> <p>2 Q. In particular, in this case, you're</p> <p>3 not offering an opinion that the levels of NDMA</p> <p>4 and NDEA that were detected in the valsartan at</p> <p>5 issue were such that they would exceed the</p> <p>6 metabolic capacity of the liver, correct, sir?</p> <p>7 A. I doubt that they would. I believe</p> <p>8 that they would be metabolized in the liver.</p> <p>9 That's why it was interesting to see that the</p> <p>10 study from Germany, the insurance study, showed</p> <p>11 liver cancer. But we already discussed that.</p> <p>12 Q. And I didn't ask that part of the</p> <p>13 question, sir.</p> <p>14 A. No, you did not.</p> <p>15 Q. Thank you.</p> <p>16 Doctor, do you agree that once NDMA</p> <p>17 is metabolized by the -- the PY450E1 enzyme that</p> <p>18 that metabolite is very reactive?</p> <p>19 Do you agree with that statement?</p> <p>20 A. One of them is, the methane</p> <p>21 diazohydroxide that everybody concentrates on</p> <p>22 because that's what damages DNA, but there's</p> <p>23 another metabolite that's formed and it's</p> <p>24 formaldehyde, which is also a carcinogen --</p> <p>25 Q. Yes, sir, and --</p>	<p style="text-align: right;">Page 332</p> <p>1 Q. To your knowledge, has that study</p> <p>2 been done?</p> <p>3 A. No.</p> <p>4 Q. Based on --</p> <p>5 A. In humans, it has not.</p> <p>6 Q. Has it been done anywhere that you</p> <p>7 can point to, Doctor?</p> <p>8 A. I don't think it's been done in</p> <p>9 animals either, but, I mean, it could be done in</p> <p>10 animals. We have looked at DNA damage from the</p> <p>11 formaldehyde produced in NDMA metabolism. We did</p> <p>12 that study. But of course in rats, you can just</p> <p>13 give NDMA and we compare to treat it with a</p> <p>14 control. The other way to do is it label NDMA.</p> <p>15 Q. Okay.</p> <p>16 Well, thank you for that.</p> <p>17 But to be clear, the state of the</p> <p>18 science today, you nor anyone else can distinguish</p> <p>19 between endogenously formed formaldehyde DNA</p> <p>20 adduct and an adduct formed as a result of</p> <p>21 formaldehyde from the metabolism of NDMA; isn't</p> <p>22 that correct?</p> <p>23 A. It hasn't been done, but it can be</p> <p>24 done. We're going to do it.</p> <p>25 Q. A lot of projects coming out of this</p>
<p style="text-align: right;">Page 331</p> <p>1 A. -- and paid much less attention to.</p> <p>2 Q. I'm sorry.</p> <p>3 A. Much less attention has been paid to</p> <p>4 the formaldehyde which cannot only damage DNA, but</p> <p>5 can cross link DNA.</p> <p>6 Q. Yes, sir.</p> <p>7 You are aware, of course, that</p> <p>8 formaldehyde is endogenously produced, correct?</p> <p>9 A. Yes.</p> <p>10 Q. It would be impossible for you or any</p> <p>11 other scientist to distinguish between</p> <p>12 endogenously-induced formaldehyde DNA damage from</p> <p>13 formaldehyde DNA damage as a result of NDMA</p> <p>14 metabolism, correct?</p> <p>15 A. No. Incorrect.</p> <p>16 Q. You can spot the difference between</p> <p>17 an endogenous formaldehyde and an NDMA</p> <p>18 formaldehyde, sir?</p> <p>19 A. Yes.</p> <p>20 Q. And how do you do that?</p> <p>21 A. Well, I would have to have a label in</p> <p>22 the NDMA that people took into their bodies and</p> <p>23 then the formaldehyde that's released would be</p> <p>24 labeled and I could determine how much came from</p> <p>25 NDMA.</p>	<p style="text-align: right;">Page 333</p> <p>1 deposition, I see.</p> <p>2 Doctor, you would agree that the NDMA</p> <p>3 once metabolized -- and you've agreed it's</p> <p>4 reactive -- it's going to attach, if you will,</p> <p>5 invade the first cell that it can get into that's</p> <p>6 close by, correct?</p> <p>7 A. The metabolite or the parent NDMA?</p> <p>8 Q. The metabolite. We're talking about</p> <p>9 the mutation that results. It's the --</p> <p>10 A. The metabolite, other than</p> <p>11 formaldehyde, methane diazohydroxide is very short</p> <p>12 lived, so that's going to hit almost where it's</p> <p>13 formed.</p> <p>14 Q. Doctor, you would agree that</p> <p>15 approximately 95% of our DNA is "junk DNA," isn't</p> <p>16 it, sir?</p> <p>17 MR. SLATER: Objection.</p> <p>18 You can answer.</p> <p>19 A. I don't know.</p> <p>20 Q. Let me ask it this way: You agree</p> <p>21 that it is approximately only 5% of DNA is coding</p> <p>22 DNA.</p> <p>23 Are you familiar with that term?</p> <p>24 A. Yes.</p> <p>25 Q. And you agree that only if coding DNA</p>

<p style="text-align: right;">Page 334</p> <p>1 is mutated that goes on checked, that's the only 2 DNA that could result in a malignant 3 transformation; agreed? 4 A. That's the theory, yes. 5 Q. If the mutated NMDA -- let me strike 6 that. 7 If the metabolized NMDA [sic] reacts 8 quickly to a cell nearby and it's junk DNA, it's 9 not going to have any ill health effects 10 regardless. 11 Correct, sir? 12 MR. SLATER: Objection. 13 You can answer. 14 A. I don't know. 15 Q. Okay. 16 Because you're not a genotoxic 17 impurities expert, correct? 18 A. Well, I'm not a microbiologist, if 19 that's what you're asking. 20 Q. You are not a genetic -- 21 A. I don't know whether an effect on 22 so-called junk DNA is necessarily innocuous. 23 Q. Yes, sir. 24 Can we agree you're not a DNA repair 25 expert?</p>	<p style="text-align: right;">Page 336</p> <p>1 effect." 2 Correct? 3 A. Probably to assert its carcinogen. 4 Q. And you're -- 5 A. I don't know whether the toxicity of 6 NDMA is necessarily related to the methylating 7 species as opposed to formaldehyde. I don't think 8 that's known. 9 Q. Doctor, what percentage of the NDMA 10 metabolizes to formaldehyde as opposed to the 11 methylating species? 12 A. One hundred percent. 13 Q. So 100% is formaldehyde and 100% is 14 this methylating species? 15 A. Yes. 16 Q. Two halves equal three? Doctor, how 17 can two things both be 100%? 18 A. For each? Okay. Maybe I wasn't too 19 clear, but for each molecule -- let's put it this 20 way: The first thing that happens is that the 21 methyl -- hold on a second, please. 22 MR. FOWLER: Yes, sir. 23 (Discussion off the stenographic 24 record) 25 THE WITNESS: I'm back.</p>
<p style="text-align: right;">Page 335</p> <p>1 A. Yes. 2 MR. SLATER: Objection. 3 MR. FOWLER: I wasn't quite done with 4 that Gombar article. If we could put up what 5 was 24, I want to look further at 4369. I'll 6 let you know when to take that down. I've 7 got a few questions, please. 8 THE VIDEOGRAPHER: What do you mean 9 by 2369? Sorry. 10 MR. FOWLER: 4369 is the page. 11 THE VIDEOGRAPHER: I'm sorry. 12 I thought you said 20. 13 MR. FOWLER: I probably did. 14 BY MR. FOWLER: 15 Q. Okay. 16 You see the first full paragraph 17 begins "We have attempted ..."? 18 A. Yeah, barely. 19 Q. Yes, sir. There it goes. 20 MR. SLATER: Can we blow that up, 21 please? 22 MR. FOWLER: I think it's blown up. 23 Q. Doctor, it states "It is well 24 established that NDMA must be metabolized to the 25 ultimate methylating species to exert its toxic</p>	<p style="text-align: right;">Page 337</p> <p>1 A. So the first thing that happens is 2 that the P450 catalyzes the hydroxylation of the 3 methyl group to give it alpha hydroxymethyl 4 dimethylnitrosamine. That intermediate has a 5 lifetime of a few seconds and it decomposes 6 spontaneously to formaldehyde and methane 7 diazohydroxide. Methane diazohydroxide is the 8 methylating agent in its DNA and the formaldehyde 9 is formaldehyde. 10 So for every molecule of NDMA that is 11 metabolized, you get one molecule of formaldehyde 12 and one molecule of methane diazohydroxide, 13 methylating agent. 14 THE WITNESS: Hold on a second. 15 MR. FOWLER: Yes, sir. 16 THE WITNESS: Okay. 17 Q. Does the formaldehyde form the 18 O6-methylguanine mutation, sir? 19 A. No. That comes from the methylating 20 agent. 21 Q. Yes, sir. 22 In any of the literature that you've 23 relied upon in your report or that you've reviewed 24 and is not part of your report, has any literature 25 about NDMA -- let's talk about the dietary</p>

<p style="text-align: right;">Page 338</p> <p>1 studies.</p> <p>2 Has any literature ever blamed the</p> <p>3 formaldehyde as being a carcinogenic factor to --</p> <p>4 let me leave it at that -- as being a carcinogenic</p> <p>5 factor in those studies?</p> <p>6 A. No. In general it's not, no. That's</p> <p>7 true.</p> <p>8 Q. Okay.</p> <p>9 A. No literature. It doesn't mean that</p> <p>10 it doesn't play a role. Nobody has thought of it.</p> <p>11 Q. Okay.</p> <p>12 A. Maybe they thought about it, but if</p> <p>13 they thought about it, they didn't do anything</p> <p>14 about it.</p> <p>15 Q. Fair enough, sir.</p> <p>16 Let's scroll down that page just a</p> <p>17 little bit further. Right above the formula, the</p> <p>18 paragraph starts "In spite of ..."</p> <p>19 Doctor, you see this statement, "In</p> <p>20 general, the smaller species" -- and we're talking</p> <p>21 about the Dr. Gombar's pharmacokinetic studies on</p> <p>22 things like beagles, hamsters and monkeys even --</p> <p>23 it states "In general, the smaller species tended</p> <p>24 to show lower bioavailability than larger</p> <p>25 species."</p>	<p style="text-align: right;">Page 340</p> <p>1 A. No, I didn't.</p> <p>2 Q. If you look -- the last paragraph on</p> <p>3 this page -- I'm sorry. In that column, sir --</p> <p>4 you see wide interspecies -- there you go, that</p> <p>5 last one in the first column. Perfect.</p> <p>6 It states "The wide interspecies</p> <p>7 difference in bioavailability in NDMA is difficult</p> <p>8 to explain."</p> <p>9 Do you see that, Doctor?</p> <p>10 A. Yes.</p> <p>11 Q. You would agree that there's</p> <p>12 interspecies differences with humans compared to</p> <p>13 any of the animals Dr. Gombar studied with his PK</p> <p>14 analysis.</p> <p>15 Correct, sir?</p> <p>16 A. Sure.</p> <p>17 Q. Doctor, do you believe that the lung</p> <p>18 plays any role in the clearance of NDMA?</p> <p>19 A. Administered orally?</p> <p>20 Q. Yes, sir.</p> <p>21 A. It seems unlikely, but it could.</p> <p>22 Q. If we could look to the last</p> <p>23 paragraph in the second column, do you agree with</p> <p>24 the statement, Doctor, that it is an</p> <p>25 oversimplification to focus solely on</p>
<p style="text-align: right;">Page 339</p> <p>1 Any dispute there, sir?</p> <p>2 A. No.</p> <p>3 Q. And Doctor, you see if it's assumed</p> <p>4 that NDMA is cleared solely by hepatic metabolism,</p> <p>5 the bioavailability will depend upon the clearance</p> <p>6 and the hepatic blood flow.</p> <p>7 You agree with that as well, right?</p> <p>8 A. Sure.</p> <p>9 Q. And is the blood flow in primates --</p> <p>10 in particular, the hepatic blood flow in</p> <p>11 primates -- the same, greater, lesser than humans,</p> <p>12 sir?</p> <p>13 A. I don't know.</p> <p>14 Q. Wouldn't it be important to</p> <p>15 understanding anything you want to extrapolate</p> <p>16 from these pharmacokinetic studies to understand</p> <p>17 what the hepatic blood flow is in --</p> <p>18 A. Probably. Probably would be.</p> <p>19 So what's your point?</p> <p>20 Q. That you didn't -- while you're</p> <p>21 relying on these for the statement that in humans</p> <p>22 there's high systemic clearance and high oral</p> <p>23 bioavailability, you didn't make any effort to</p> <p>24 determine whether that data can be fairly</p> <p>25 extrapolated from the Gombar studies, did you?</p>	<p style="text-align: right;">Page 341</p> <p>1 pharmacokinetics when you're trying to do a risk</p> <p>2 assessment, if you will, of NDMA's</p> <p>3 bioavailability?</p> <p>4 A. Sure. It's complicated.</p> <p>5 Q. But it says to base risk on dose</p> <p>6 alone is also an oversimplification.</p> <p>7 Do you agree with that, sir?</p> <p>8 A. Well, sure, but I mean, you know,</p> <p>9 dose response is very important in carcinogenesis.</p> <p>10 You know, this Gombar study was published before</p> <p>11 the Peto study, if I'm not mistaken.</p> <p>12 So, I mean, we do know a lot about</p> <p>13 the dose response characteristics of NDMA in</p> <p>14 laboratory animals, particularly rats. Also mice</p> <p>15 and hamsters. So we know a lot about that, so I</p> <p>16 mean, you know, this very general statement here</p> <p>17 was probably made in response to a reviewer, so,</p> <p>18 you know, just because something is written like</p> <p>19 in the discussion session of a paper doesn't mean</p> <p>20 that it's necessarily engraved in stone. So sure,</p> <p>21 it's an oversimplification to focus solely on</p> <p>22 pharmacokinetics.</p> <p>23 MR. FOWLER: We can take that exhibit</p> <p>24 down.</p> <p>25 Q. Doctor, returning to your statement</p>

<p style="text-align: right;">Page 342</p> <p>1 on page eight of your report where you were 2 attempting to opine that NDMA has a high systemic 3 clearance and high oral bioavailability in humans, 4 the only studies that you're pointing to, if we 5 look at sites 21, 22, 23, 24, 25, it's Gombar, 6 Gombar, Gombar, then a Dr. Anderson article. 7 Is that the -- is there anything 8 else, sir, to support an opinion that there's high 9 systemic clearance and high oral bioavailability 10 of NDMA? 11 A. There are other articles, yeah. I 12 don't think I got them all here. There's quite a 13 bit of literature on pharmacokinetics and NDMA. 14 You know, I was a little selective here. This is 15 not a comprehensive review. But, you know, 16 systemic clearance by the liver is kind of a 17 common observation. 18 Q. You would agree, Doctor, that the 19 systemic clearance in oral bioavailability depends 20 on the dose, correct? 21 A. Yes. 22 Q. And you can point to no study that 23 evaluates a low dose of NDMA and NDEA and arrives 24 at any conclusion about its bioavailability or 25 systemic clearance.</p>	<p style="text-align: right;">Page 344</p> <p>1 question, sir. I think you've answered -- 2 MR. SLATER: Counsel, I'm not looking 3 to argue with you or anything. I just want 4 to establish something so I understand. 5 I asked the videographer how long 6 we're at at this point and how long 7 Mr. Fowler has been going. I think it's 8 probably 45 minutes approximately. 9 MR. FOWLER: We don't have to guess. 10 What's the number? How long have we been on 11 the record? 12 THE VIDEOGRAPHER: If you guys 13 wouldn't mind, I could go off the record so I 14 could give you an exact number. 15 MR. FOWLER: Apparently, that's 16 important right now, so let's do that. 17 THE VIDEOGRAPHER: The time is 6:27. 18 We're going off the video record. 19 (Recess taken) 20 THE VIDEOGRAPHER: The time is 6:33. 21 This begins media seven. 22 You may proceed. 23 Q. Doctor, switching gears again, sir, 24 with regard to the FDA workshop that you 25 participated in, did FDA provide you with any</p>
<p style="text-align: right;">Page 343</p> <p>1 Fair statement? 2 MR. SLATER: Objection. 3 You can answer. 4 A. No, that's wrong. You're just 5 talking about all kinds of low-dose studies. 6 Q. Do those studies speak to 7 bioavailability, sir? 8 A. Sure they did, yeah. 9 Q. Bioavailability is -- 10 A. When, you know, you have a low dose 11 given to a rat and it's orally and it's 12 metabolized significantly in the liver, then the 13 bioavailability of the test compound to other 14 tissues is very low. 15 Q. Any such data would have to be 16 extrapolated to humans based upon the hepatic 17 blood flow, correct, sir? 18 A. Well, sure. 19 Q. Any dose given to a mouse or any 20 rodent or other species would have to be adjusted 21 to evaluate a low dose in humans, correct? 22 MR. SLATER: Objection. 23 Lack of foundation. 24 You can answer. 25 MR. FOWLER: Let me withdraw the</p>	<p style="text-align: right;">Page 345</p> <p>1 written materials in advance or even the questions 2 in advance, sir? 3 A. Yes, the questions. 4 Q. Did you share those questions with 5 anyone? 6 A. No. 7 Q. What has been marked as Exhibit 12, 8 the FDA's summary on that workshop, sir, did you 9 get -- did you get an advance copy to review and 10 comment upon? 11 MR. SLATER: Wasn't he questioned on 12 this document already, sir? So now you're 13 going back into the FDA document? Okay. 14 You can answer the question. 15 I'm writing to the court. 16 A. Yes. I'm not sure what you mean by 17 advance copy. 18 Q. Did you get a draft to review and 19 comment before FDA published it to the -- 20 A. Yes. Yes. 21 Q. And did you take the opportunity to 22 review it? 23 A. Yes. 24 Q. Did you have any comments or changes? 25 A. Nothing -- nothing substantial. I</p>

<p style="text-align: right;">Page 346</p> <p>1 may have had some minor changes, but in general, 2 it was a good summary. 3 Q. How did you communicate those changes 4 to FDA? 5 A. Email with the -- I forgot her name 6 right now. 7 Q. That's fine, sir. 8 Did you send a red line document or 9 did you type some summary in an email? 10 A. Summary in an email. 11 MR. SLATER: Just for the record, I 12 object to this entire line of questioning. 13 This document was thoroughly addressed by 14 Mr. Trischler, so this is clearly 15 duplicative. 16 The fact that you may be finding a 17 different question that's not identical to 18 Mr. Trischler's doesn't mean that this 19 shouldn't be left alone, as Mr. Trischler 20 covered this subject. 21 You could continue. 22 Q. Do you still have that email, Doctor? 23 A. I don't know. 24 Q. I will just make a request on the 25 record -- and I'll follow up with counsel -- that</p>	<p style="text-align: right;">Page 348</p> <p>1 Sources of Human Exposure." I believe it may 2 be 13. Do you mind if I put 13 up to 3 confirm? 4 MR. FOWLER: Yes, please. 5 THE VIDEOGRAPHER: This is Exhibit 6 13. 7 MR. FOWLER: Okay. Thank you. 8 Q. I'll direct your attention to page 9 four, last paragraph. 10 Doctor, you recall the discussion 11 about endogenous and exogenous sources of NDMA? 12 Do you recall that, sir? 13 A. Yes. 14 Q. Do you recall the FDA's statement "To 15 calculate the risk, it's imperative to determine 16 endogenous formation and understand the 17 pharmacokinetics of nitrosamine formation and 18 distribution"? 19 A. Yes. 20 Q. We were just speaking to the 21 pharmacokinetic -- 22 MR. SLATER: Counsel, why are you 23 rehashing? This document and this subject 24 was already addressed by Mr. Trischler. 25 Again, this is duplicative.</p>
<p style="text-align: right;">Page 347</p> <p>1 we'd like a copy of the email with your edits to 2 the draft summary statement. 3 A. I don't think they were specific, but 4 anyhow, I'd have to go back and look. 5 Q. Fair enough -- 6 A. It wasn't, like, line 35, change this 7 to that. In general -- 8 Q. Okay. That's helpful. Yes, sir. 9 A. -- I agreed with her summary. Very 10 comprehensive. 11 Q. Right, but you indicated you did have 12 changes and you did communicate back to FDA with 13 regard to your response to the draft, correct? 14 A. I believe so. 15 Q. I'll make that request offline, sir. 16 At the time that you reviewed the FDA 17 summary, did you have the transcripts available to 18 you? 19 A. I didn't review the transcripts. 20 MR. FOWLER: Now, let's put up 21 Exhibit 12, the FDA summary. Just a couple 22 things I wanted to clarify from your prior 23 testimony. 24 THE VIDEOGRAPHER: Counsel, I have as 25 Exhibit 12 the "Critical Review of Major</p>	<p style="text-align: right;">Page 349</p> <p>1 Q. Do you agree that it's important to 2 understand the endogenous formation and the level 3 of endogenous formation? Correct? 4 A. Yes. 5 Q. And you -- during the panel, when the 6 question is presented to the group, each of you 7 has an opportunity to respond to the question at 8 hand, correct? 9 MR. SLATER: Objection. 10 A. Actually, it was very directed, so I 11 mean certain people -- it was all outlined 12 beforehand who was supposed to respond to which 13 questions and when. It was very scripted. Not 14 scripted, but -- I don't know. I can't think of 15 the word. But basically, you were told when to 16 speak. 17 Q. Doctor, you would agree that the body 18 sees an NDMA molecule as is and doesn't 19 distinguish its origin, whether it be from food, 20 endogenous or from pharmaceuticals, correct? 21 MR. SLATER: Objection. 22 You can answer. 23 A. Yes. 24 Q. And the cumulative exposure that 25 contributes to the response is the essential part</p>

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<p>1 of the valuation.</p> <p>2 Would you agree with that?</p> <p>3 MR. SLATER: Objection.</p> <p>4 A. Yes.</p> <p>5 MR. SLATER: Cumulative exposure was</p> <p>6 discussed earlier as well, counsel.</p> <p>7 Q. Doctor, you believe that the --</p> <p>8 strike that.</p> <p>9 During the testimony, you were given</p> <p>10 an opportunity to respond on the question of</p> <p>11 endogenous formation.</p> <p>12 Do you recall what you testified you</p> <p>13 believe the level was?</p> <p>14 MR. SLATER: Again, objection.</p> <p>15 This has been covered. Mr. Trischler</p> <p>16 went through that presentation.</p> <p>17 You can answer.</p> <p>18 I'm continuing to type my email to</p> <p>19 the court. I regret it that this is</p> <p>20 necessary.</p> <p>21 Q. Doctor, do you recall what you</p> <p>22 testified to the levels of endogenous formation</p> <p>23 being?</p> <p>24 A. I don't recall the exact thing, but,</p> <p>25 you know, the literature indicates that there is</p>	<p>1 A. Correct.</p> <p>2 Q. So you answered your questions --</p> <p>3 MR. SLATER: Counsel, can we stop for</p> <p>4 a second? I apologize --</p> <p>5 MR. FOWLER: No, we can't stop today.</p> <p>6 We can't stop right now. I'm in the middle</p> <p>7 of a question.</p> <p>8 MR. SLATER: I object, Counsel.</p> <p>9 You're not -- this isn't -- I'm really just</p> <p>10 telling you -- I need to tell you you have on</p> <p>11 the transcript -- or on the screen the same</p> <p>12 transcript and you're asking about bias,</p> <p>13 which he was questioned about already.</p> <p>14 So that's the third area where you're</p> <p>15 now in the same question. Therefore, we're</p> <p>16 going to stop the deposition. This email is</p> <p>17 going to go to Judge Vanaskie and I'm asking</p> <p>18 to terminate the deposition because of this</p> <p>19 conduct --</p> <p>20 MR. FOWLER: I'm reclaiming my time.</p> <p>21 Q. Directing your attention to page --</p> <p>22 MR. SLATER: We're done.</p> <p>23 MR. FOWLER: No, we're not.</p> <p>24 MR. SLATER: Go off the record.</p> <p>25 I'm stopping the deposition and we're</p>
Page 351	Page 353
<p>1 considerable endogenous formation of nitrosamines</p> <p>2 that are not metabolized. So my -- excuse me.</p> <p>3 Q. Yes, sir.</p> <p>4 A. My thinking was that we should really</p> <p>5 learn more about the endogenous formation of</p> <p>6 nitrosamines such as NDMA that are metabolized and</p> <p>7 that was the point I was trying to make at the FDA</p> <p>8 meeting.</p> <p>9 MR. FOWLER: Thank you. Let's take</p> <p>10 down this exhibit. Please put up the day one</p> <p>11 transcript.</p> <p>12 Q. Doctor, when you were testifying at</p> <p>13 the FDA panel, you understood that your words were</p> <p>14 being transcribed just as they are today, correct,</p> <p>15 sir?</p> <p>16 A. Yes.</p> <p>17 Q. And while you weren't under oath, it</p> <p>18 was your -- you were certainly doing your best to</p> <p>19 speak the scientific truth, correct?</p> <p>20 A. Yes.</p> <p>21 Q. And you said earlier -- several</p> <p>22 times, I think -- that you had no bias coming into</p> <p>23 that panel, notwithstanding your retention by</p> <p>24 Mr. Slater.</p> <p>25 Do you recall that?</p>	<p>1 going to wait for Judge Vanaskie --</p> <p>2 MR. FOWLER: I'm in the middle of a</p> <p>3 question with this witness.</p> <p>4 Q. Page 159, please --</p> <p>5 MR. SLATER: No, you're not. You're</p> <p>6 done.</p> <p>7 Dr. Hecht, don't answer the question.</p> <p>8 This is harassing and in violation of</p> <p>9 Judge Vanaskie's order.</p> <p>10 I'm going to email him. Hopefully</p> <p>11 he'll be available and then we'll go from</p> <p>12 there.</p> <p>13 MR. FOWLER: I'm going to make a</p> <p>14 proffer on the record that I'm attempting to</p> <p>15 show that the doctor's testimony at this FDA</p> <p>16 hearing is completely inconsistent with his</p> <p>17 testimony today.</p> <p>18 I'm entitled to show him this</p> <p>19 transcript and ask him why he testified</p> <p>20 differently at the FDA.</p> <p>21 MR. SLATER: I'm directing him not to</p> <p>22 answer.</p> <p>23 MR. FOWLER: If you want to call the</p> <p>24 Judge on that, we can.</p> <p>25 MR. SLATER: Please stop the record.</p>

<p style="text-align: right;">Page 354</p> <p>1 I'm writing to Judge Vanaskie.</p> <p>2 MR. FOWLER: I would further proffer</p> <p>3 I have additional questions based on the</p> <p>4 doctor's testimony at the FDA hearing, I have</p> <p>5 questions based upon the doctor's testimony</p> <p>6 with regard to the Peto study, among others,</p> <p>7 and moreover, I have questions about</p> <p>8 Dr. Hecht's testimony with regard to</p> <p>9 Dr. Johnson's PDE and the threshold.</p> <p>10 I have areas to cover that have not</p> <p>11 been fully explored.</p> <p>12 I'm asking you to reconsider letting</p> <p>13 us finish this deposition --</p> <p>14 MR. SLATER: I'm writing to the</p> <p>15 judge.</p> <p>16 MR. FOWLER: I don't -- you can keep</p> <p>17 telling me that, Adam. I'm asking you to</p> <p>18 reconsider and let us finish this deposition.</p> <p>19 I don't think we're wasting anyone's time</p> <p>20 other than right now.</p> <p>21 MR. SLATER: You can't commit to a</p> <p>22 stop time. You want to be able to go on</p> <p>23 forever --</p> <p>24 MR. FOWLER: How can I commit to a</p> <p>25 stop time, Adam? I've never heard you commit</p>	<p style="text-align: right;">Page 356</p> <p>1 Okay.</p> <p>2 MS. KAPKE: Five to ten probably.</p> <p>3 Maybe not even that long.</p> <p>4 MR. SLATER: I'm just changing my</p> <p>5 email. Thank you.</p> <p>6 THE VIDEOGRAPHER: Counsel, would</p> <p>7 everyone like me to go off the video?</p> <p>8 MS. LOCKARD: Yes. Off the record.</p> <p>9 And can you give us a count of how long we've</p> <p>10 been going?</p> <p>11 This is Victoria Lockard speaking.</p> <p>12 THE VIDEOGRAPHER: The time is 6:45.</p> <p>13 We're going off the video record.</p> <p>14 (Recess taken)</p> <p>15 THE VIDEOGRAPHER: The time is now</p> <p>16 657.</p> <p>17 This begins media eight.</p> <p>18 You may proceed.</p> <p>19 MR. FOWLER: Can I please get that</p> <p>20 exhibit back? Day one transcript, FDA panel.</p> <p>21 Please turn to page 159.</p> <p>22 Q. When we stopped, Doctor, I was asking</p> <p>23 you if you recalled what you said at the time of</p> <p>24 the panel about the endogenous production.</p> <p>25 Let me direct you to lines 16 to 20.</p>
<p style="text-align: right;">Page 355</p> <p>1 to a stop time --</p> <p>2 MR. SLATER: Sorry. You're so angry.</p> <p>3 Don't be so angry. I'm just trying to --</p> <p>4 MR. FOWLER: You've been screaming</p> <p>5 since I started questioning this witness.</p> <p>6 MR. SLATER: You know, I feel bad for</p> <p>7 the court reporter.</p> <p>8 I don't know what to tell you. If</p> <p>9 you want me to talk, I will. If you want to</p> <p>10 talk, you can. But I'm trying to type and</p> <p>11 email on my iPhone.</p> <p>12 I think that the ruling has been</p> <p>13 violated. I think I have good grounds for a</p> <p>14 protective order. I'm asking for one.</p> <p>15 THE VIDEOGRAPHER: Would both sides</p> <p>16 like me to go off the video record?</p> <p>17 MR. SLATER: Do you have my proffer,</p> <p>18 Madam Court Reporter?</p> <p>19 THE COURT REPORTER: I have what you</p> <p>20 guys have been saying.</p> <p>21 MR. FOWLER: Fair enough. Thank you.</p> <p>22 MS. KAPKE: This is Kara Kapke. I</p> <p>23 also have a few follow-up questions, but they</p> <p>24 should not last more than ten to 15 minutes.</p> <p>25 MR. SLATER: Ten to fifteen minutes?</p>	<p style="text-align: right;">Page 357</p> <p>1 You state "So I think with regard to</p> <p>2 the question of endogenous formation, which is</p> <p>3 critical here because there are really high levels</p> <p>4 in endogenous formation, maybe we do not have to</p> <p>5 be that concerned about the low levels present in</p> <p>6 drugs."</p> <p>7 Have I read your testimony correctly,</p> <p>8 Dr. Hecht?</p> <p>9 A. Yes.</p> <p>10 MR. SLATER: Before you answer,</p> <p>11 Doctor, objection.</p> <p>12 I'm asking you to put the full page</p> <p>13 up there so Dr. Hecht can see the full</p> <p>14 context, not just this little snippet. Let's</p> <p>15 give him the whole page, let's let him see</p> <p>16 the context and --</p> <p>17 MR. FOWLER: Absolutely.</p> <p>18 Q. So Doctor, the lead-up question for,</p> <p>19 as you recall, had to do with the endogenous</p> <p>20 formation of NMDA [sic] and speaking about the</p> <p>21 biomarkers and the adducts.</p> <p>22 The question before you responded was</p> <p>23 "Can we have more discussion of what you think of</p> <p>24 all the biomarkers that you have discussed today</p> <p>25 that could be more appropriate for nitrosamines?"</p>

<p style="text-align: right;">Page 358</p> <p>1 As your counsel said, you start your</p> <p>2 answer "I think DNA adducts would be good to look</p> <p>3 at. You think we have the technology to reliably</p> <p>4 quantify DNA adducts with high-res mass</p> <p>5 spectrometry and we also have the knowledge based</p> <p>6 on years of study about artifact formation."</p> <p>7 Then you state what you said about</p> <p>8 the endogenous formation.</p> <p>9 Does this refresh your recollection</p> <p>10 of how you characterized the endogenous formation</p> <p>11 of NDMA at the FDA panel, sir?</p> <p>12 A. Yes.</p> <p>13 MR. SLATER: Objection.</p> <p>14 Before you answer, Doctor, please let</p> <p>15 me object.</p> <p>16 Objection. Okay? Objection. Lack</p> <p>17 of foundation. It's a very misleading</p> <p>18 question, but we'll come back to it,</p> <p>19 Mr. Fowler. You and I both know that.</p> <p>20 You can answer, Dr. Hecht.</p> <p>21 Q. Doctor, do you recall this discussion</p> <p>22 at the FDA panel?</p> <p>23 A. Yes.</p> <p>24 Q. And do you recall the issue of what</p> <p>25 levels of endogenous formation NDMA there is?</p>	<p style="text-align: right;">Page 360</p> <p>1 didn't say that there was higher endogenous</p> <p>2 formation or that there was lower endogenous</p> <p>3 formation. I didn't say any of these things.</p> <p>4 What I said was that we need to</p> <p>5 develop the technology, the research to assess</p> <p>6 endogenous formation. That way, we would be able</p> <p>7 to know whether the endogenous formation of</p> <p>8 compounds like dimethylnitrosamine really was.</p> <p>9 Right now, we don't know what it is.</p> <p>10 So that was my -- that was a message I was trying</p> <p>11 to deliver.</p> <p>12 Q. Have you completed your response,</p> <p>13 Doctor?</p> <p>14 A. Yes.</p> <p>15 MR. FOWLER: Can I have that sentence</p> <p>16 that begins with "So ..." blown up, now that</p> <p>17 we've seen the whole page?</p> <p>18 MR. SLATER: I'd like to keep the</p> <p>19 whole page on the screen, frankly, because</p> <p>20 now we can't see the full context.</p> <p>21 Q. Doctor, can you read if we don't blow</p> <p>22 that up okay?</p> <p>23 A. Yes.</p> <p>24 Q. Okay.</p> <p>25 You see the sentence "So I think with</p>
<p style="text-align: right;">Page 359</p> <p>1 A. Not NDMA in particular. So what I</p> <p>2 was referring to in that panel discussion was that</p> <p>3 there's significant of data for the endogenous</p> <p>4 formation of nitrosoproline and other nitrosamines</p> <p>5 that are not metabolized. We could determine this</p> <p>6 by simply measuring other levels in urine after</p> <p>7 giving people the precursors and sodium nitrite,</p> <p>8 as an example.</p> <p>9 For dimethylnitrosamine and other</p> <p>10 dialkyl nitrosamines, which are extensively</p> <p>11 metabolized, we don't know how much endogenous</p> <p>12 formation there is and what I was trying to say in</p> <p>13 the FDA meeting was that what a real need that we</p> <p>14 have is to develop the technology by which we</p> <p>15 would be able to accurately determine how much</p> <p>16 endogenous formation there was of compounds like</p> <p>17 dimethylnitrosamine.</p> <p>18 So, you know, I was speculating. I</p> <p>19 speculated that the amount that's formed</p> <p>20 endogenously might be greater than the exogenous</p> <p>21 amounts, but we don't know and that was my point.</p> <p>22 We need research. That was my point. Nothing</p> <p>23 else.</p> <p>24 Q. Have you completed --</p> <p>25 A. I didn't say that there was -- I</p>	<p style="text-align: right;">Page 361</p> <p>1 regard to the question of endogenous formation</p> <p>2 ..." that we were looking at?</p> <p>3 A. Yes.</p> <p>4 Q. Okay.</p> <p>5 You state "which is critical here."</p> <p>6 Are you talking about here being the</p> <p>7 issue with NDMA and valsartan?</p> <p>8 MR. SLATER: Objection.</p> <p>9 Lack of foundation.</p> <p>10 A. No. I was talking about generally.</p> <p>11 Okay? Not necessarily about valsartan. I was</p> <p>12 talking about generally for nitrosamines.</p> <p>13 Okay?</p> <p>14 Q. Okay, sir.</p> <p>15 A. We know --</p> <p>16 Q. You've answered the question --</p> <p>17 MR. SLATER: Stop.</p> <p>18 Please continue to answer, Doctor.</p> <p>19 A. Let me finish?</p> <p>20 Q. Certainly, Doctor.</p> <p>21 A. We know from a significant amount of</p> <p>22 data that there is endogenous formation,</p> <p>23 nitrosoproline and other nitrosamines that are not</p> <p>24 metabolized. We can determine this readily. It</p> <p>25 has been done. There's a lot of solid data out</p>

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<p>1 there. We don't have this data for the dialkyl 2 nitrosamines that are sensibly metabolized such as 3 dimethylnitrosamine. We don't have the data. 4 So we don't know whether endogenous 5 formation of dimethylnitrosamine is zero or 6 whether it's the same as the exogenous exposure or 7 more. We don't know. 8 That was my point. So how it's 9 written, how you interpret what's written, I don't 10 know. But that was my point. 11 Q. Thank you, Doctor. 12 Help me understand the last part of 13 that sentence, please. "Maybe we do not have to 14 be that concerned about the low levels that are 15 present in drugs." 16 Did I read that correctly? 17 A. Yes. 18 Q. And we're talking about the NDMA 19 levels in the valsartan that you're there at the 20 panel for, correct? 21 A. That's right. 22 MR. SLATER: Lack of foundation. 23 Q. Thank you. Did we get that answer -- 24 A. As I tried to explain, sir, we don't 25 know. Okay? What I was trying to say in that</p>	<p>1 A. Four hundred micrograms of what and 2 which colleague? 3 Q. Doctor -- well, I'll not pronounce 4 his name right. It starts with a K. Doctor -- 5 can you help me, sir? 6 A. Kokkinakis. 7 Q. Yes, sir. 8 Do you recall the slides that he put 9 up at the FDA panel on endogenous formation? 10 A. Yes, I don't agree with those at all. 11 I think they're flawed. 12 Q. Right. 13 To your point, Doctor, if the level 14 is high -- and would you agree a level greater 15 than 100 micrograms a day would be considered high 16 in the context that you and I are speaking of now? 17 A. Yes. 18 Q. The point is if it's that high and we 19 add 10, 15, 20 micrograms to that endogenous 20 supply of NDMA, you would not consider that to be 21 an increased risk of cancer compared to the 22 endogenous source, correct? 23 MR. SLATER: Objection. 24 A. I don't know what you're talking 25 about, risk of cancer. I don't know. I mean, the</p>
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<p>1 panel discussion was that we need to develop the 2 technology and do the experiments so we can find 3 out the extent of formation of -- of endogenous 4 formation -- of dimethylnitrosamine and other 5 dialkyl nitrosamines that are rapidly metabolized. 6 That's what I was trying to say. 7 Q. Yes, I've gotten that, Doctor. I'm 8 focused now on how you concluded the sentence, 9 that "Maybe we don't have to be concerned about 10 the low levels present in the drugs." 11 Can you explain that, please? 12 A. You're not listening because I have 13 explained it. Okay? Listen to what I'm saying. 14 Okay? 15 If the amount of endogenous formation 16 of dimethylnitrosamine turn out to be very high, 17 then we wouldn't have to be concerned. But we 18 don't know. 19 Q. Thank you, Doctor. 20 A. We don't know. We have zero data. 21 Q. Well, respectfully, you disagree with 22 the data that your colleague presented at the FDA 23 panel as to the level of 400 micrograms in the -- 24 produced endogenously. 25 You just disagreed with that.</p>	<p>1 point is -- the point that I'm making -- and this 2 is what I believe. Okay? 3 In this deposition, we don't have 4 reliable data on endogenous formation of 5 dimethylnitrosamine and until we have that data, 6 we cannot say that the exogenous formation such as 7 through valsartan is unimportant. We can't say 8 that because we don't have the data. The data 9 that Kokkinakis quoted, I do not believe it's 10 correct. 11 Q. Doctor, do you agree that the panel 12 and FDA was concerned that it would make no sense 13 to the public, including the scientific informed 14 public like yourself, that if FDA set a limit of 15 NDMA at, like, 96 nanograms and the body is 16 producing 400 micrograms a day, that it could 17 erode the confidence in FDA's risk assessments 18 because that would make no sense to the public? 19 Do you recall that discussion? 20 MR. SLATER: Objection. 21 A. Well, sure it would, but we don't 22 have the data. 23 Q. Right. 24 A. If we had -- if we had reliable 25 accepted data on, you know, that NDMA was formed</p>

<p style="text-align: right;">Page 366</p> <p>1 to the extent of 400 micrograms per day in humans, 2 then FDA would not have put out the thing about 3 96 nanograms. 4 Q. Did FDA impanel this workshop so that 5 they might understand and get scientific input 6 from leaders in the different areas about what 7 these levels are? Isn't that why it was one of 8 the questions posed? 9 A. Yes. 10 MR. FOWLER: Let me have day two 11 transcript, please. 12 Q. Directing your attention to page 15, 13 we're going to look at line nine through 18. It 14 states here, Doctor -- I hope you can see it 15 because I don't want to blow it up, I want to 16 leave the whole page there. 17 It states that the balance of 18 evidence seems to be that the amount consumed by 19 the drugs -- consumed in drugs is minuscule or at 20 least very much smaller than one expects from 21 intake in water and especially in foods and I 22 think it would send a confusing message to 23 consumers, citizens in general, to tell them that 24 the body somehow knows whether a given molecule, 25 any given nitrosamine comes from a drug taken by</p>	<p style="text-align: right;">Page 368</p> <p>1 MR. SLATER: Counsel, stop. 2 A. That's why they made the 3 96 nanograms. 4 MR. SLATER: Counsel, we're going to 5 stop the deposition. 6 A. I mean, really, honestly, we have 7 been -- we have been through this before. 8 MR. FOWLER: I honestly couldn't hear 9 either one of you. 10 THE WITNESS: I'm starting to agree 11 with Adam. 12 MR. FOWLER: I couldn't hear Adam or 13 you, sir. 14 MR. SLATER: Judge Vanaskie has just 15 asked to call -- Mr. Fowler, we're 16 breaking -- let's go off the record. 17 Judge Vanaskie has asked us to 18 include him in a phone conference and he gave 19 the number. We need to call him. I don't 20 have a call in number that I can give to 21 anyone, so I don't know what to do. We got 22 to get him on the phone. He wants to speak 23 right now. 24 THE VIDEOGRAPHER: Would you like to 25 go off the video first?</p>
<p style="text-align: right;">Page 367</p> <p>1 necessity or food voluntarily. 2 Do you see that, Doctor? 3 A. Yes. 4 MR. SLATER: Objection. 5 Lack of foundation. 6 Inaccurately read. 7 Q. You don't disagree with that, Doctor, 8 right? That's what you and I have been speaking 9 about? 10 MR. SLATER: Objection. 11 A. We need the data. You know, we need 12 the data. Intake from water is very unclear and 13 endogenous formation is very unclear. 14 The only place where we really have 15 reliable data, you know, other than valsartan and 16 the other drugs obviously is food. 17 Q. Yes, sir. 18 But my question was actually do you 19 agree that the issue here was that it could send a 20 confusing message if FDA is setting an acceptable 21 intake limit that is far below what our body 22 creates naturally? 23 That's my question, sir. 24 A. Sure, but we don't have the data and 25 they know that. They know that --</p>	<p style="text-align: right;">Page 369</p> <p>1 MR. SLATER: That's fine. 2 THE VIDEOGRAPHER: The time is 7:12. 3 We're going off the video record. 4 (Recess taken) 5 THE VIDEOGRAPHER: The time is now 6 727. 7 This begins media nine. 8 You may proceed. 9 Q. Dr. Hecht, do you have an opinion 10 whether or not NDMA is a threshold compound? 11 Do you understand the question? 12 A. Threshold compound? You mean whether 13 there's a threshold for carcinogenicity? 14 Q. Yes, sir. 15 MR. SLATER: Objection. 16 Asked and answered. 17 You can answer. 18 A. I don't know of any evidence that 19 there is. 20 Q. Do you have an opinion one way or the 21 other, sir? 22 A. I believe there is no threshold based 23 on the studies of Peto, Grasso and others. 24 MR. FOWLER: Well, let's mark -- 25 A. The large rat dose response study.</p>

<p style="text-align: right;">Page 370</p> <p>1 They concluded that there was no indication of a 2 threshold. 3 MR. FOWLER: Let's mark Peto 1991 B. 4 Q. Doctor, while that's being called up 5 here, I think we're -- as far as our nomenclature 6 goes, I think we're in agreement that a threshold 7 level is one below which there's no evidence of 8 carcinogenicity. Just so we're on the same page, 9 sir. 10 A. Yes. 11 THE VIDEOGRAPHER: Counsel, just 12 wanted to check. The document, I just want 13 to check. 14 The document you're looking for, does 15 it have at the top of the page "Cancer 16 Research"? 17 MR. FOWLER: It does. It's called 18 "Dose and Time Relationships for Tumor 19 Induction in the Liver and Esophagus," etc. 20 THE VIDEOGRAPHER: Let me know if 21 this is the right one here. 22 MR. FOWLER: No. 23 THE VIDEOGRAPHER: Okay. 24 MR. FOWLER: It's 1991 A. 25 Q. Doctor, while this is coming up, do</p>	<p style="text-align: right;">Page 372</p> <p>1 Q. And would you defer to a genetic 2 toxicologist to interpret such data when 3 calculating a PDE? 4 MR. SLATER: Objection. 5 You can answer. 6 A. A genetic toxicologist? 7 Q. Yes, sir. 8 A. Would I defer to a genetic 9 toxicologist? I'm not sure. 10 Q. You've never done a benchmark dose 11 evaluation, have you, sir? 12 A. I think I mentioned this repeatedly 13 today. 14 MR. FOWLER: Just waiting on Peto, 15 sir. I'm just trying not to -- 16 THE VIDEOGRAPHER: Counsel, I only 17 have one document, the one that I pulled up, 18 that was labeled with P-E-T-O for Peto. 19 MR. FOWLER: Okay, sir. I'll forge 20 ahead without it. 21 Q. Doctor, do you recall that in the 22 Peto study, there was a level of -- let me start 23 that again. 24 The Peto study was a large cancer 25 bioassay, correct?</p>
<p style="text-align: right;">Page 371</p> <p>1 you agree that the concept, if you will, of 2 permissible daily exposure of PDE, the PDE itself 3 is a level below which -- let me start that again. 4 The PDE would be considered a 5 threshold level in that nomenclature, sir? 6 MR. SLATER: Objection. 7 This topic was asked and answered and 8 covered earlier. 9 You can answer. 10 A. Repeat the question. 11 Q. Is a PDE another term for a threshold 12 level? 13 A. Essentially, yes. 14 Q. I understand you did not read 15 Dr. Johnson's article, so is it fair to say that 16 you don't know whether that article establishes 17 any sort of threshold, sir? 18 A. Which article was that? 19 Q. Dr. Johnson's 2021 -- 20 A. I hadn't read that, no. 21 Q. Yes, sir. 22 So you're not here to say whether or 23 not that data demonstrates a threshold at low 24 doses? 25 A. I'm not, no.</p>	<p style="text-align: right;">Page 373</p> <p>1 A. Yes. 2 Q. It administered a variety of doses, 3 some of which until that animal died, correct? 4 A. Yes. 5 Q. And it had a control group, yes? 6 A. Yes. 7 Q. And at low doses, if the number of 8 subject animals produced fewer tumors than the 9 background rate of the control group, would you 10 say that there's evidence of a -- that that 11 supports evidence of a threshold? 12 Do you understand my question, sir? 13 A. No. 14 Q. It was a bad question. I'll try 15 again. 16 If the dose levels from let's say 17 0.001 through 0.087, as reflected in table seven 18 of Peto, produced tumors fewer than the control 19 group expressed, do you agree that you cannot 20 attribute the tumors produced at those low doses 21 to anything other than background? 22 MR. SLATER: Objection. 23 I object for multiple reasons, 24 including you're quoting a table that nobody 25 can see and I object to the multiple parts of</p>


<p style="text-align: right;">Page 374</p> <p>1 the question.</p> <p>2 You can answer if you can.</p> <p>3 A. I really can't answer that without</p> <p>4 looking at the data. But I do recall very</p> <p>5 specifically that Peto said either in the abstract</p> <p>6 or in the discussion that there was no evidence of</p> <p>7 a threshold, quote, unquote.</p> <p>8 Peto is a statistician who was very</p> <p>9 well respected, so I take his word.</p> <p>10 Q. Yes, sir.</p> <p>11 Doctor, if in an animal study the</p> <p>12 doses produce fewer tumors than the control group,</p> <p>13 can you conclude anything about the causation of</p> <p>14 those low doses, sir?</p> <p>15 A. I would have to look at the data. I</p> <p>16 don't know what data you're talking about.</p> <p>17 Q. Is there any conceivable study that</p> <p>18 you can imagine where the dose group revealed</p> <p>19 fewer tumors than the control group and a</p> <p>20 causation determination can be made? Can you</p> <p>21 envision anything like that, sir?</p> <p>22 MR. SLATER: Objection.</p> <p>23 Multiple reasons.</p> <p>24 You can answer.</p> <p>25 A. I don't know.</p>	<p style="text-align: right;">Page 376</p> <p>1 contaminated valsartan (see below) the formation</p> <p>2 of these DNA adducts would be sufficient to cause</p> <p>3 mutations in cancer in exposed humans."</p> <p>4 Have I read that correctly, sir?</p> <p>5 A. Yes.</p> <p>6 Q. You would agree, sir, that the number</p> <p>7 of adducts is dispositive for a cell to undergo a</p> <p>8 malignant transformation; isn't that correct?</p> <p>9 A. Is dispositive? What was your -- I</p> <p>10 didn't hear --</p> <p>11 Q. I'll rephrase, sir.</p> <p>12 A. The number of adducts is what?</p> <p>13 Q. There is a minimum number of adducts</p> <p>14 that must be -- that exist in a cell before it</p> <p>15 undergoes a malignant transformation, correct?</p> <p>16 A. A minimum number? Sure. I mean,</p> <p>17 there is a number. We don't necessarily know what</p> <p>18 it is.</p> <p>19 Q. Yes, sir. And one O6-methylguanine</p> <p>20 mutation can be the result of one metabolized NDMA</p> <p>21 molecule, right?</p> <p>22 A. Correct.</p> <p>23 Q. Do you have any reason to dispute</p> <p>24 that there are roughly 600 adducts of</p> <p>25 O6-methylguanine at any given time in a cell</p>
<p style="text-align: right;">Page 375</p> <p>1 Q. Why are control groups used in animal</p> <p>2 studies, sir?</p> <p>3 A. Because it gives you a reference</p> <p>4 point to compare to your treated group.</p> <p>5 Q. And why is that important?</p> <p>6 A. Because, you know, there might be</p> <p>7 some tumors that form in the untreated animals for</p> <p>8 reasons other than the material that you're</p> <p>9 administering due to other factors, endogenous</p> <p>10 factors and whatever.</p> <p>11 So you have to have a control group</p> <p>12 because, you know, tumors will develop in various</p> <p>13 organs of animals with old age, laboratory animals</p> <p>14 with old age, so you need the control group as a</p> <p>15 comparison.</p> <p>16 Q. Thank you, sir.</p> <p>17 Let me direct your attention --</p> <p>18 shifting gears back to your report, please -- I'm</p> <p>19 going to direct your attention to page 11.</p> <p>20 Let me know when you're there, sir.</p> <p>21 A. I'm there.</p> <p>22 Q. The middle paragraph -- and this is</p> <p>23 Exhibit 1 -- in the middle paragraph, at the</p> <p>24 bottom, you state "Given sufficient exposure to</p> <p>25 NDMA and NDEA, as with the levels found in the</p>	<p style="text-align: right;">Page 377</p> <p>1 absent exogenous NDMA?</p> <p>2 A. Where did you get that from?</p> <p>3 Q. My question is do you have any reason</p> <p>4 to dispute that, sir?</p> <p>5 A. Yes.</p> <p>6 Q. What is your basis?</p> <p>7 A. I don't know where you got that</p> <p>8 number from. Just made it up or what? Where did</p> <p>9 you get the number 600 from?</p> <p>10 Q. You agree there's a baseline number</p> <p>11 of O6-methylguanine adducts in a cell at any given</p> <p>12 time, sir, right?</p> <p>13 A. Baseline number? What is that?</p> <p>14 THE WITNESS: Hold on, sir.</p> <p>15 (Discussion off the stenographic</p> <p>16 record)</p> <p>17 Q. I'll move on, Doctor.</p> <p>18 A. Sorry.</p> <p>19 Q. Referring to page 11, I'm just</p> <p>20 interested in what the number of DNA adducts you</p> <p>21 are referring to in that sentence.</p> <p>22 You don't give any level, sir, and</p> <p>23 that's what I'm asking --</p> <p>24 A. Which sentence now?</p> <p>25 Q. The one we read in page 11 of your</p>

<p style="text-align: right;">Page 378</p> <p>1 report, "Given sufficient exposure to NDMA and 2 NDEA, as with the levels found in the valsartan, 3 the formation of these DNA adducts would be 4 sufficient to cause mutations." 5 My question is how many adducts, sir? 6 A. I don't know. One. One adduct in 7 theory. 8 Q. I'm sorry. You broke up. 9 One more time? 10 A. One adduct in theory is enough. 11 Q. You would agree that one adduct is 12 subject to DNA repair, correct? 13 A. Yes. 14 Q. And if repaired, no risk of 15 carcinogenicity, correct? 16 A. Not from that particular pathway, 17 correct. 18 Q. Do you disagree that DNA repair can 19 and does create a threshold level when exposed to 20 low doses of NDMA? 21 MR. SLATER: Objection. 22 You can answer. 23 A. It's a very general question. I 24 mean, there's no doubt that DNA repair is 25 important. You know, when you say does it affect</p>	<p style="text-align: right;">Page 380</p> <p>1 dose response; isn't that correct, sir? 2 MR. SLATER: Objection. 3 You can answer. 4 A. That depends what you mean by 5 qualifications. I'm not a toxicologist. That's 6 true. I don't know that that necessarily excludes 7 me from having opinions. 8 Q. Yes, sir. 9 Would you defer to a toxicologist as 10 to the existence of a threshold for NDMA and NDEA? 11 MR. SLATER: Objection. 12 You can answer. 13 A. That would depend who the 14 toxicologist was. 15 Q. Fair point, sir. Thank you. 16 Doctor, do you agree that or disagree 17 that the DNA adducts that we're speaking about, 18 this O6-methylguanine, those adduct measurements 19 do not define the location of the adduct in the 20 genome. 21 Is that a true statement? 22 A. Yes. 23 Q. Given that cells have evolved 24 efficient measures to keep gene coding sequences 25 damage free, it's not possible to currently say if</p>
<p style="text-align: right;">Page 379</p> <p>1 the low doses, you know, what's a low dose, what 2 are the conditions. There are many factors, but 3 we know that DNA repair is important. 4 You know, there's a lot of hand 5 waving in your statement. 6 Q. Thank you, sir. 7 I've now found where the 600 came 8 from -- I apologize -- earlier. 9 Were you familiar with an article by 10 Dr. Krause and McKeene, et al, from 2019 entitled 11 "Immunological and Mass Spectrometry Approaches to 12 Determine Thresholds of Mutagenic DNA Adduct 13 O6-methylguanine and VBo"? 14 Are you familiar with that article, 15 sir? 16 A. Doesn't strike a bell offhand. 17 Q. Okay. 18 Thank you, sir. 19 Doctor, do you agree that potency, 20 the existence of a threshold and dose response are 21 toxicology issues, sir? 22 A. Yes. 23 Q. And because you are not a 24 toxicologist, you're not qualified to render 25 opinions on potency existence of a threshold or</p>	<p style="text-align: right;">Page 381</p> <p>1 DNA adducts accrue in a linear fashion in the 2 coding sequences. 3 Do you agree with that? 4 A. Yeah, yes. 5 Q. And for the jury -- I'm sorry. 6 A. Yeah. 7 Q. For the jury's purpose, by saying it 8 does not accrue in a linear fashion, that means if 9 you're adding two more NDMA molecules that it will 10 not -- let me start that again. 11 If you double the NDMA molecules, it 12 doesn't result in a linear uptick of the 13 mutations, correct, sir? 14 MR. SLATER: Objection. 15 You can answer. 16 A. You know, that's a complicated 17 question because we know that the dose response 18 for NDMA -- and NNK, for that matter -- in mice is 19 a hockey stick -- 20 Q. Yes, sir. 21 A. -- kind of picture because when the 22 O6-methylguanine DNA methyl transfer is 23 succeeded -- in the activity that is succeeded -- 24 then the cancerous mutations will increase more 25 rapidly, so it's not linear. It's more like this.</p>

<p style="text-align: right;">Page 382</p> <p>1 Q. And a hockey stick, I've got a couple 2 behind me, they're long and flat and then the 3 blade goes up at the end, correct, sir? It's a 4 line with an uptick at the end where the hockey 5 blade would be? That's how it gets its name? 6 A. Yes. You have a slowly increasing 7 amount which would be similar to the blade and 8 then when you reach a certain point, the increase 9 is greater, so that's where the hockey stick comes 10 from. 11 Q. Yes, sir. Thank you. 12 Shifting gears a little bit, Doctor, 13 just to keep moving, do you agree that if more 14 than one nitrosamine are present -- let's do it 15 this way. 16 If NDEA and NDMA are both present in 17 the body at the same time, do you agree that their 18 actions, if you will, will be additive and not 19 synergistic? 20 Do you understand the question, sir? 21 A. Yes, probably. But to tell the 22 truth, I don't think we have good data on that. 23 MR. FOWLER: Can I have the FDA 24 transcript, day one please? 25 (Whereupon, Exhibit 25 was marked for</p>	<p style="text-align: right;">Page 384</p> <p>1 Q. You're not -- you have no -- you're 2 not disagreeing with yourself here today, are you, 3 sir? 4 A. No. 5 MR. FOWLER: Doctor, let me again 6 switch gears. You could take that down, 7 please. 8 Q. With regard to your research on 9 tobacco and cigarette smoking, the -- you would 10 agree that there are -- there have been identified 11 specific cancers which are attributed to cigarette 12 smoking, correct, sir? 13 A. Yes. 14 Q. And I think you testified earlier 15 there's some 70 carcinogens in tobacco, which 16 include certain nitrosamines, yes? 17 MR. SLATER: Objection. 18 A. In tobacco smoke. 19 MR. SLATER: Objection. 20 We're now duplicating questioning 21 exactly. I don't appreciate it. 22 MR. FOWLER: It's just a foundation, 23 Counsel. Trying to orient the doctor as I 24 jump around here. 25 Q. So Doctor, the carcinogens from</p>
<p style="text-align: right;">Page 383</p> <p>1 identification.) 2 (Whereupon, Exhibit 26 was marked for 3 identification.) 4 Q. Do you recall this issue coming up in 5 the FDA panel, sir? 6 A. Not right now, I don't, but sure, I 7 probably do. 8 Q. I'll try to refresh your 9 recollection. Look at day one and I'll direct 10 your attention, please, to page 143 and in 11 particular, directing you to line 15 through 19. 12 Do you see your name there? 13 A. Yes. 14 Q. I could have it blown up so you could 15 take your time to look at it. 16 So you say "I agree. Considering the 17 low levels that we are going to be observing, 18 additivity is definitely the default assumption of 19 the molar amounts that are present, so I agree 20 with everything that has been said about 21 additivity." 22 Do you see that, sir? 23 A. Yes. 24 Q. And are you familiar -- I'm sorry? 25 A. That's what I said.</p>	<p style="text-align: right;">Page 385</p> <p>1 cigarette smoke, you would agree, are quickly -- 2 quickly enter the bloodstream upon exposure. 3 Do you agree with that? 4 A. Yes. 5 Q. And as a result of -- 6 A. For the most part. 7 Q. Fair enough. 8 As a result, they travel throughout 9 the body's tissues, the arterial system, back, 10 venous system. 11 It's everywhere, correct, sir? 12 A. It's a very general statement. You 13 know, each carcinogen behaves differently. For 14 example, some may be retained in the lung 15 particles. There may be other factors that affect 16 the absorption into the bloodstream. 17 Q. Based upon your research, Doctor, you 18 agree that NDMA, as one of those nitrosamines, 19 likewise enters the blood and is transported to 20 various tissue systems in the blood, correct? 21 A. Yes. 22 Q. And throughout your research of 23 cigarette smoke and tobacco, none of your studies 24 or any studies that you have seen has identified 25 cigarette smoke-induced tumors as being caused by</p>

<p style="text-align: right;">Page 386</p> <p>1 NDMA.</p> <p>2 Isn't that true?</p> <p>3 A. Correct.</p> <p>4 Q. In fact, it's been your publication</p> <p>5 that the nitrosamines NNN, NNK and there may be a</p> <p>6 couple more, are the responsible nitrosamines for</p> <p>7 the cancers that cigarette smoking causes.</p> <p>8 Is that a fair statement?</p> <p>9 A. No. I've never excluded other</p> <p>10 nitrosamines.</p> <p>11 Q. Okay.</p> <p>12 A. I presented data that supports the</p> <p>13 concept that NNN and NNK cause DNA damage and</p> <p>14 cancer in smokers and also smokeless tobacco</p> <p>15 users, but I've never excluded other nitrosamines</p> <p>16 whatsoever.</p> <p>17 Q. Thank you for that clarification,</p> <p>18 sir.</p> <p>19 Can you explain why it is if NDMA is</p> <p>20 transported through the blood from the cigarette</p> <p>21 smoke why there's not any evidence that NDMA</p> <p>22 causes cancer in these various tissues that it</p> <p>23 reaches through the cigarette smoke as a result of</p> <p>24 the cigarette smoke, sir?</p> <p>25 MR. SLATER: Objection.</p>	<p style="text-align: right;">Page 388</p> <p>1 A. Well, you were talking about</p> <p>2 causation.</p> <p>3 Q. Yes, sir.</p> <p>4 A. So, you know, the first thing in</p> <p>5 causation is usually epidemiology.</p> <p>6 Q. For cancers that are known to be</p> <p>7 caused by cigarette smoke, sir, have the</p> <p>8 determinations as to the specific types of cancer,</p> <p>9 to your knowledge, been evaluated in a -- by</p> <p>10 pathologists in the laboratory to reach any</p> <p>11 conclusions at all, sir?</p> <p>12 A. Repeat your question.</p> <p>13 Q. Well, outside of epidemiology</p> <p>14 evidence, I'm trying to understand whether the</p> <p>15 causal link between cigarette smoke and these</p> <p>16 cancers that you've identified has been identified</p> <p>17 through toxicology studies of human tissue in in</p> <p>18 vivo, in vitro, but using human tissue to make</p> <p>19 that determination?</p> <p>20 A. Yes, absolutely.</p> <p>21 Q. Okay. And -- I'll just leave it at</p> <p>22 that.</p> <p>23 No, I won't.</p> <p>24 There's no such similar study with</p> <p>25 regard to any determination of NDMA and any</p>
<p style="text-align: right;">Page 387</p> <p>1 You can answer.</p> <p>2 A. We don't know the answer to that.</p> <p>3 Q. You agree that the nitrosamines in</p> <p>4 tobacco smoke or smokeless tobacco have different</p> <p>5 carcinogenic presentations when administered</p> <p>6 differently, correct?</p> <p>7 A. Yes and no. It's not really correct.</p> <p>8 It depends -- you can't generalize. Okay? I know</p> <p>9 too much about this. Some of them -- NNK for</p> <p>10 example, will affect the lung almost independent</p> <p>11 of the root of administration, seemingly given by</p> <p>12 insulation into the bladder and affects mainly the</p> <p>13 lung. NNN, on the other hand, will affect the</p> <p>14 oral cavity and esophagus when given in drinking</p> <p>15 water.</p> <p>16 Q. I'm sorry.</p> <p>17 A. It's hard to generalize.</p> <p>18 Q. For each cancer that you would agree</p> <p>19 is caused by cigarette smoke, do you agree that</p> <p>20 that determination was based upon actual data and</p> <p>21 testing and an evaluation of human tissue and</p> <p>22 tumors to make that causation connection?</p> <p>23 A. Epidemiology, yes.</p> <p>24 Q. Well, I'm speaking of actual lab</p> <p>25 science, Doctor.</p>	<p style="text-align: right;">Page 389</p> <p>1 cancers that it could allegedly cause in humans,</p> <p>2 correct?</p> <p>3 A. Oh, there are multiple studies of</p> <p>4 NDMA metabolism by human tissues, organ culture</p> <p>5 studies. Also, sub cellular fractions. Yes,</p> <p>6 multiple studies published many years ago.</p> <p>7 Q. Notwithstanding the agreement today,</p> <p>8 Doctor, you said several times that the level of</p> <p>9 NDMA in the pharmaceuticals should be zero?</p> <p>10 A. Yes.</p> <p>11 Q. Doctor, you don't hold yourself out</p> <p>12 as any sort of regulatory expert, do you, sir?</p> <p>13 A. No.</p> <p>14 Q. Do you know what a drug master file</p> <p>15 is?</p> <p>16 A. Not exactly.</p> <p>17 Q. Do you know what criteria FDA uses</p> <p>18 whether or not to approve a drug?</p> <p>19 A. That's not my area.</p> <p>20 Q. So you have no basis for saying</p> <p>21 whether or not these drugs have been approved or</p> <p>22 not or if that number should be zero, do you?</p> <p>23 MR. SLATER: Objection.</p> <p>24 A. I have a basis for saying it should</p> <p>25 be zero. I absolutely have a -- I absolutely have</p>

<p style="text-align: right;">Page 390</p> <p>1 a basis for saying it should be zero because I've 2 looked at the method of synthesis and I've looked 3 at all the data from CHP and the others and 4 absolutely this never should have happened. We 5 shouldn't be here. It should have been zero. 6 MR. FOWLER: Thank you, Doctor. 7 I don't have further questions. I'll 8 pass the witness to the next questioner. 9 Thank you so much for your time and patience. 10 MR. SLATER: You know, if you told me 11 you had a hockey stick, we would have been 12 more easy going. I don't want to get hit by 13 a hockey stick. 14 MS. KAPKE: Good evening, Dr. Hecht. 15 I'll be very brief. I have a couple of 16 questions. 17 EXAMINATION BY 18 MS. KAPKE: 19 Q. You agreed in response to 20 Mr. Trischler's questions earlier today that 21 valsartan is typically a long-term drug taken 22 chronically. 23 Do you remember that? 24 A. Yes. 25 MR. SLATER: Objection.</p>	<p style="text-align: right;">Page 392</p> <p>1 incidence of tumors. 2 Q. Let's just use that study. I'll just 3 follow up on that. 4 How long of a duration of exposure 5 did the rats have in the Peto study? 6 A. Over two years, I believe it was. 7 Q. Are there any studies that you are 8 relying on that are acute animal studies? 9 A. There are single dose studies of 10 NDMA. Sure. 11 Q. And are -- could you give me -- are 12 they cited in your report? 13 A. No. My report doesn't go into detail 14 and all of the literature on NDMA, which is very 15 extensive, the carcinogenicity literature -- 16 Q. Okay. Let me just back up -- 17 A. -- they're out there. I mean, 18 there's a huge number of studies on NDMA 19 carcinogenicity and laboratory animals. 20 Q. Okay. 21 Let me just back up and ask it this 22 way: You've agreed here multiple times that dose 23 and duration are important. 24 Is there a minimum number of days a 25 person would need to take valsartan that contain</p>
<p style="text-align: right;">Page 391</p> <p>1 Duplicative. 2 Q. Understanding that valsartan is 3 typically taken chronically, do you have an 4 opinion about whether acute usage of valsartan 5 containing an NDMA or NDEA impurity could cause a 6 person to develop cancer? 7 MR. SLATER: Objection. 8 You can answer. 9 A. Well, it would be more likely from 10 continuous use because, you know, the cumulative 11 dose would be greater. 12 Q. Did you evaluate the animal studies 13 with an eye towards duration of use to make an 14 assessment of how long a person would need to take 15 valsartan containing NDMA or NDEA before that NDMA 16 or NDEA exposure could have caused the person to 17 develop cancer? 18 A. Which animal studies? 19 Q. Any of them. 20 A. No, I didn't attempt to make that 21 evaluation. There are many -- there are many 22 animal studies of NDMA. I guess the one that's 23 most compelling is the Peto study. So we know 24 that very low doses of NDMA given over a long 25 period of time to rats can cause a significant</p>	<p style="text-align: right;">Page 393</p> <p>1 NDMA or NDEA in any amount that's relevant to this 2 case before that exposure would cause a person to 3 develop cancer? 4 A. We don't know. In theory, one 5 exposure is sufficient. We don't know a minimum 6 number of days. We don't know that. 7 Q. Are there any studies that you are 8 relying on specifically to allow you to 9 extrapolate to duration of use for only a single 10 day as being appropriate to cause cancer in a 11 human? 12 A. No. I don't believe there is any 13 study like that in a human. 14 Q. Are there any -- 15 A. There are single dose studies in 16 animals -- 17 Q. And -- 18 A. -- of NDMA. 19 Q. Are any of those studies sufficient 20 for you to extrapolate to a person who took one 21 pill of valsartan containing NDMA or NDEA and NDMA 22 or NDEA impurity? Can you cite me any such study 23 that is appropriate to extrapolate? 24 A. No, there's not. 25 Q. What about the same question for a</p>

<p style="text-align: right;">Page 394</p> <p>1 single prescription fill for 30 days?</p> <p>2 A. I don't have that kind of data. That</p> <p>3 would be -- that would be speculation.</p> <p>4 Q. And --</p> <p>5 A. It's all dose response, so obviously</p> <p>6 the more frequently the pill contaminated with</p> <p>7 dimethylnitrosamine was taken, the higher the</p> <p>8 risk.</p> <p>9 Q. Would it be fair to say that a person</p> <p>10 needed to take valsartan containing an NDMA or</p> <p>11 NDEA impurity for at least a year before that NDMA</p> <p>12 or NDEA exposure could have caused that person to</p> <p>13 develop cancer? Would that be a fair statement?</p> <p>14 A. I don't think we know the timeframe.</p> <p>15 I mean, the study that we talked about before from</p> <p>16 Germany covered three years, I believe, and they</p> <p>17 saw an increased risk of liver cancer, but I don't</p> <p>18 think we know the timeframe. I mean, in theory,</p> <p>19 everything lines up wrong. You know, one dose</p> <p>20 should be enough in theory.</p> <p>21 Q. Well, in --</p> <p>22 A. If everything is wrong, I mean, you</p> <p>23 know, if your DNA repair is not working right, if</p> <p>24 you happen to hit the right part of the DNA in the</p> <p>25 right gene, the right mutation, in theory, it only</p>	<p style="text-align: right;">Page 396</p> <p>1 A C K N O W L E D G M E N T</p> <p>2</p> <p>3 I, STEPHEN HECHT, Ph.D., hereby certify that I</p> <p>4 have read the transcript of my testimony taken under oath</p> <p>5 in my examination of August 17, 2021; that the transcript</p> <p>6 is a true, complete and correct record of what was asked,</p> <p>7 answered and said during this deposition, and that the</p> <p>8 answers on the record as given by me are true and</p> <p>9 correct.</p> <p>10 _____</p> <p>11 STEPHEN HECHT, Ph.D.</p> <p>12</p> <p>13 Signed and subscribed to</p> <p>14 before me, this day of</p> <p>15 2021.</p> <p>16 _____</p> <p>17 Notary Public</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p style="text-align: right;">Page 395</p> <p>1 takes one.</p> <p>2 Q. Well, what I want to get at is what</p> <p>3 is your opinion to a reasonable degree of medical</p> <p>4 and scientific certainty as to the duration of</p> <p>5 exposure that can cause a person to develop cancer</p> <p>6 following an exposure to valsartan containing an</p> <p>7 NDMA or NDEA impurity.</p> <p>8 I'm trying to see if you can put a</p> <p>9 duration limit on that for me to a reasonable</p> <p>10 degree of medical and scientific certainty.</p> <p>11 A. It's very hard to do but, you know,</p> <p>12 if you force me to give a timeframe, I guess as a</p> <p>13 minimum I would be, you know, comfortable with one</p> <p>14 year, but it's very -- very difficult question to</p> <p>15 answer.</p> <p>16 MS. KAPKE: Okay. I have no further</p> <p>17 questions. Thank you.</p> <p>18 MR. SLATER: Let's go off the record.</p> <p>19 THE VIDEOGRAPHER: The time is 8:05.</p> <p>20 We're going off the video record.</p> <p>21 (Time noted: 8:05 p.m.)</p> <p>22 (Deposition concluded for the</p> <p>23 evening.)</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 397</p> <p>1 C E R T I F I C A T I O N</p> <p>2 I, SARA K. KILLIAN, RPR, CCR, do</p> <p>3 hereby certify that STEPHEN HECHT, Ph.D.</p> <p>4 the witness whose examination under oath</p> <p>5 is hereinbefore set forth, was duly sworn,</p> <p>6 and that such deposition is a true record</p> <p>7 of the testimony given by such witness.</p> <p>8 I FURTHER CERTIFY that I am not</p> <p>9 related to any of the parties to this</p> <p>10 action by blood or marriage, and that</p> <p>11 I am in no way interested in the</p> <p>12 outcome of this matter.</p> <p>13 IN WITNESS WHEREOF, I have hereunto</p> <p>14 set my hand this 23rd day of August, 2021.</p> <p>15</p> <p>16</p> <p>17</p> <p>18 </p> <p>19 SARA K. KILLIAN, RPR, CCR</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

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1 ERRATA SHEET
2 VERITEXT NEW JERSEY REPORTING, LLC
3 CASE NAME: In re: valsartan
4 DATE OF DEPOSITION: 8/17/2021
5 WITNESS' NAME: STEPHEN HECHT, Ph.D.
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STEPHEN HECHT, Ph.D.
SUBSCRIBED AND SWORN TO
BEFORE ME THIS _____ DAY
OF _____, 2021.
NOTARY PUBLIC
MY COMMISSION EXPIRES _____

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY.

THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

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Exhibit 3

FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

Get updates on the recalls

Update: 11/13/2019 - FDA warns Mylan for CGMP deviations

Update [11/13/2019] Today, the U.S. Food and Drug Administration posted a [warning letter \(/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019\)](#) to Mylan Pharmaceuticals, Inc. in Chodavaram Village, Vizianagaram, Andhra Pradesh, India. Mylan manufactures valsartan active pharmaceutical ingredient (API) and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several current good manufacturing practice (CGMP) deviations at this Mylan facility, including failure to have adequate written procedures for the receipt, identification and handling of raw materials and failure to adequately clean equipment and utensils. Failure to correct these deviations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 10/15/2019 - FDA warns Torrent for CGMP violations

Update [10/15/2019] Today, the U.S. Food and Drug Administration posted a [warning letter \(/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019\)](#) to Torrent Pharmaceuticals in Ahmedabad, Gujarat, India. Torrent manufactures losartan potassium tablets and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several manufacturing violations at Torrent's Taluka-Kadi, Indrad, Gujarat facility, including failure to follow written procedures for production and process control and failure to adequately investigate batch discrepancies. Failure to correct these violations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 9/20/2019 - Torrent expands its voluntary recall of losartan

Update [9/20/2019] Torrent Pharmaceuticals is expanding its voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-o\)](#) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\) \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](#) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications

Go to [FDA Statement \(/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications\)](#).

6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA

Update [6/26/2019] FDA is alerting patients and health care professionals to Macleods Pharmaceuticals' voluntary [recall](/safety/recalls-market-withdrawals-safety-alerts/macleods-pharmaceutical-limited-issues-voluntary-nationwide-consumer-level-recall-losartan-potassium) of two lots of losartan potassium tablets (50mg strength) and 30 lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets (12 lots of 50mg/12.5mg strength, three lots of 100mg/12.5mg strength, and 15 lots of 100mg/25mg strength). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs). The agency also updated the list of [recalled angiotensin II receptor blockers \(ARBs\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

6/12/2019: UPDATE - Teva expands its voluntary recall of losartan

Update [6/12/2019] Teva Pharmaceuticals is expanding its voluntary [recall](/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-expands-voluntary-nationwide-recall-losartan-potassium-50-mg-and-100-mg) to include seven additional lots of losartan potassium tablets (three lots of 50 mg strength and four lots of 100 mg strength) labeled by Golden State Medical Supply. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and), accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA

Update [5/6/2019] FDA is alerting patients and health care professionals to a voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/vivimed-life-sciences-pvt-ltd-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-50-mg-and>) of 19 lots of losartan potassium tablets made by Vivimed Life Sciences Pvt Ltd in Alathur, Chennai, India and distributed by Heritage Pharmaceuticals Inc, East Brunswick, New Jersey, due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). Vivimed is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the [interim acceptable intake limit](https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2) (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2>) of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

The agency also updated the [list of recalled ARBs](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) (</drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and>).

5/2/2019: UPDATE - Laboratory analysis of valsartan products

Update [5/2/2019] FDA posted [laboratory test results showing NDEA levels in recalled valsartan products](/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) (</drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products>) as well as an assessment of the cancer risk from NDEA in valsartan.

4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA

Update [4/29/2019] FDA is alerting patients and health care professionals to a voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg>) of 44 lots of losartan potassium tablets manufactured by Teva Pharmaceuticals and labeled as Golden State Medical Supply due to the detection of the impurity N-Nitroso-N-methyl-4-

aminobutyric acid (NMBA). The recalled products were made with active pharmaceutical ingredient (API) manufactured by Hetero Labs. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Additionally, Legacy expanded its [recall \(/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets\)](/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets) to include one additional lot of losartan tablets made with API manufactured by Hetero Labs.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

The agency also updated the list of [recalled losartan medicines \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods

Update [4/19/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium>) to include 104 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

The agency updated the list of [losartan products under recall \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

FDA is also posting new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A [direct injection GC-MS method \(/media/123409/download\)](/media/123409/download) that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine

(NEIPA), and N-nitrosodibutylamine (NDBA)

- A [headspace GC-MS method \(/media/124025/download\)](/media/124025/download) that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys\)](/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys).

3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information

Update [3/22/2019] FDA has updated the [list of valsartan medicines under recall \(/media/118231/download\)](/media/118231/download) to incorporate additional repackagers of Aurobindo's valsartan-containing medicine. FDA has also updated the [list of losartan medicines under recall \(/media/119422/download\)](/media/119422/download) to include repackagers of Torrent's and Camber's losartan-containing medicines.

The agency also updated the [list of valsartan medicines not under recall \(/media/118232/download\)](/media/118232/download) accordingly.

3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market

Update [3/20/2019] To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the [interim acceptable intake limit](#) of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated. The agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the U.S. supply in approximately six months.


Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.


FDA reminds patients taking recalled losartan to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death. Untreated diabetic nephropathy (kidney disease) leads to worsening renal (kidney) disease.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA continues to work with companies and international regulators to ensure products entering the U.S. market do not contain nitrosamine impurities.

3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan

Update [3/1/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (<https://public4.pagefreezer.com/browse/FDA/02-07-2022T12:48/https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium-o>)  (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) to include 114 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Today, the agency also issued a press release (<https://public4.pagefreezer.com/browse/FDA/28-06-2022T09:52/https://www.fda.gov/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-arb-drug-products-reports-finding-new-nitrosamine>)  (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) to provide additional information about its ongoing investigation and another voluntary recall by Hetero/Camber

Pharmaceuticals, which was announced on February 28, of 87 lots of losartan potassium tablets (25 mg, 50 mg and 100 mg). The recalled losartan potassium and losartan potassium/hydrochlorothiazide tablets are also manufactured by Hetero, which are distributed by Camber, and contain the impurity NMBA.

Torrent and Hetero/Camber are only recalling lots of losartan-containing medication with NMBA above the interim acceptable intake limits of 0.96 parts per million (ppm).

The agency also updated the list of losartan products under recall (</media/119422/download>).

3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan

Update [3/1/2019] AurobindoPharma USA is expanding its voluntary recall (AurobindoPharma USA, Inc. Initiates a Voluntary Nationwide Consumer Level Recall Expansion of 38 Lots of Amlodipine Valsartan Tablets USP and Valsartan Tablets, USP due to the detection of NDEA (N-Nitrosodiethylamine) Impurity.) to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine.

Aurobindo is only recalling lots of valsartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.083 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the valsartan products under recall (</media/118231/download>).

3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall

Go to Press Release

(<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632425.htm>).

FDA updates table of interim limits for nitrosamine impurities in ARBs

Update [2/28/2019] FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96***
Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
Eprosartan	800	96	0.12	26.5	0.033	96	0.12
Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled

Update [2/25/2019] FDA is alerting patients and health care professionals to a voluntary recall of one lot of losartan potassium/hydrochlorothiazide (HCTZ) 100mg/25mg combination tablets manufactured by Macleods Pharmaceuticals. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine made with active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Macleods is only recalling lots of losartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.27 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the list of losartan products under recall (</media/119422/download>).

1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues

Go to FDA Statement (</news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps>).

1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan

Update [1/23/2019] Torrent Pharmaceuticals is further expanding its voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium>) to include six additional lots of losartan potassium and hydrochlorothiazide combination tablets, for a total of 16 lots of losartan-containing medicines. This recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan-containing medication containing NDEA above the interim acceptable intake limits of 0.27 parts per million (ppm).

The agency also updated the list of losartan medications under recall (</media/119422/download>).

1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled

Update [1/18/2019] FDA is alerting patients and health care professionals to a voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-irbesartan-and-irbesartan-hctz>) of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Princeton Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the irbesartan active pharmaceutical ingredient manufactured by Zhejiang Huahai Pharmaceuticals (ZHP).

Solco is only recalling lots of irbesartan-containing medication where NDEA has been detected above the interim limit of 0.088 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin receptor II blockers (ARBs).

The agency also updated the list of irbesartan products under recall.

1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan

Update [1/3/2019] Torrent Pharmaceuticals is expanding its voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp>) to include eight additional lots of losartan potassium tablets, for a total of 10 lots. This recall is due to trace amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan medication containing NDEA above the interim acceptable intake level of 0.27 parts per million.

The agency also updated the list of list of valsartan products under recall (</media/118231/download>).

1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA

Update [1/2/2019] FDA is alerting patients and health care professionals to Aurobindo Pharma USA's voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lots-amlodipine>) of two lots of valsartan tablets, 26 lots of amlodipine and valsartan combination tablets, and 52 lots of valsartan and hydrochlorothiazide (HCTZ) combination tablets due to the amount of N-Nitrosodiethylamine (NDEA) in the valsartan active

pharmaceutical ingredient. Aurobindo is recalling amlodipine and HCTZ only in combination medications containing valsartan. Neither amlodipine nor HCTZ is currently under recall by itself.

Aurobindo is recalling lots of valsartan-containing medication that tested positive for NDEA above the interim acceptable daily intake level of 0.083 parts per million.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above interim acceptable daily intake levels.

FDA also updated the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download).

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Some ARBs contain no NDMA or NDEA.

12/20/2018: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA

Update [12/20/2018] FDA is alerting patients and health care professionals to Torrent Pharmaceuticals'

voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium\)](/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) of two lots of losartan potassium 100 mg tablets due to N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Not all Torrent losartan-containing medications distributed in the U.S. are being recalled. Torrent is recalling only those lots of losartan medication that tested positive for NDEA above the acceptable daily intake of 0.27 ppm.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable daily intake levels.

FDA posted a list of [losartan medications under recall \(/media/119422/download\)](/media/119422/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain

NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs

Update [12/19/2018] FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

The agency evaluated safety data for N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) to determine an interim acceptable intake level for these impurities in the ARB class. NDMA and NDEA are probable human carcinogens and should not be present in drug products. We are currently aware of NDMA and NDEA in certain valsartan, irbesartan and losartan-containing products, and those products and some active pharmaceutical ingredients (API) used to manufacture them have been recalled from the U.S. market. See the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download), and the [list of irbesartan products under recall \(/media/118233/download\)](/media/118233/download).

Drug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients. The agency will use the interim limits to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects a new impurity or higher level of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients. To aid industry and regulatory agencies, FDA has developed and published methods to detect NDMA and NDEA impurities – the gas chromatography/mass spectrometry (GC/MS) headspace method (</media/115965/download>), the [combined GC/MS headspace method \(/media/117843/download\)](/media/117843/download), and the [combined GC/MS direct injection method \(/media/117807/download\)](/media/117807/download). These methods can be used for drug substances and products, and users should validate them as part of good manufacturing practices and where data are used to support a regulatory submission or required quality assessment of the API or drug product.

Not all ARB products contain NDMA or NDEA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088
Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.

12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter

Update [12/12/2018] The FDA has updated its testing methods to detect NDMA and NDEA impurities – the [GC/MS\) headspace method \(/media/115965/download\)](#), the [combined headspace method \(/media/117843/download\)](#), and the [combined direct injection method \(/media/117807/download\)](#) – by adding the limits of detection (LOD) and clarifying that the methods can be used for both drug substances and drug products. These methods were

validated with respect to valsartan drug substances and drug products, but the agency expects them to have comparable LODs and limits of quantitation (LOQ) for other angiotensin II receptor blockers (ARB).

The agency also issued a press release announcing the posting of a warning letter the agency issued Nov. 29 to Zhejiang Huahai Pharmaceuticals Co. Ltd. (ZHP).

12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications

Go to [Press Release \(/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these\)](/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these).

12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products

Update [12/6/2018] Mylan Pharmaceuticals is expanding its voluntary recall [\(\[!-\\$wcmUrl\('link','UCM627647'\)--\]\)](#) to include all lots of non-expired valsartan-containing products due to trace amounts of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient (API) manufactured by Mylan Laboratories Limited. The 104 additional lots include 26 lots of amlodipine and valsartan tablets, 51 lots of valsartan tablets and 27 lots of valsartan and hydrochlorothiazide tablets. These lots were distributed in the U.S. between March 2017 and November 2018.

The agency also updated the [list of valsartan products under recall \(/media/118231/download\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#).

11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA

Update [11/27/2018] FDA is alerting patients and health care professionals to Teva Pharmaceuticals' voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts\)](/safety/recalls-market-withdrawals-safety-alerts) of valsartan-containing products manufactured using active pharmaceutical ingredient (API) from Mylan Pharmaceuticals. Mylan voluntarily [recalled \(/safety/recalls-market-withdrawals-safety-alerts\)](/safety/recalls-market-withdrawals-safety-alerts) valsartan-containing products on November 20.

Teva is recalling all lots of amlodipine and valsartan combination tablets and amlodipine, valsartan, and hydrochlorothiazide (HCTZ) combination tablets due to the presence of N-Nitrosodiethylamine (NDEA). Teva has recalled other valsartan-containing products in

recent months due to the presence of N-Nitrosodimethylamine (NDMA). With this recall, Teva has now recalled all their unexpired valsartan-containing products from the U.S. market.

The agency continues to investigate and test all angiotensin II receptor blocker (ARBs) for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download). The agency reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA

Update [11/21/2018] FDA is alerting patients and health care professionals to Mylan Pharmaceuticals' voluntary recall of 15 lots of valsartan-containing products due to the presence of N-Nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the U.S. are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of [valsartan products under recall \(/media/118231/download\)](/media/118231/download) and [valsartan products not under recall \(/media/118232/download\)](/media/118232/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan

potassium and hydrochlorothiazide recall of one lot due to NDEA

Update [11/9/2018] FDA is alerting patients and health care professionals to Sandoz's voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-voluntary-nationwide-recall-one-lot-losartan-potassium-and-hydrochlorothiazide-due>) of one lot – JB8912 – of losartan potassium and hydrochlorothiazide 100mg/25mg tablets, that contain losartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a diuretic, used in combination for the treatment of hypertension. Sandoz's product was made using an active pharmaceutical ingredient (API) that has tested positive for NDEA. The API was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd, which is on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html).

Sandoz's losartan drug products make up less than 1 percent of the total losartan drug products in the U.S. market.

FDA continues to investigate the presence of NDEA and NDMA, which are probable human carcinogens, in ARBs and is taking swift action when it identifies unacceptable impurities in API and finished drug products.

FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDEA or NDMA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA

Certain irbesartan products labeled as Westminster Pharmaceuticals Inc. and GSMS Inc. recalled

Update [10/30/2018] FDA is alerting patients and health care professionals to ScieGen's voluntary recall of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain N-Nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen (causes cancer). FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply, Inc. (GSMS). See the list of irbesartan products under recall (</media/117814/download>). This is the first non-valsartan drug product the agency has found to contain the NDEA impurity.

ScieGen's recall affects about 1 percent of the irbesartan drug products in the U.S. market.

Additionally, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace\)](/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of their irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or N-Nitrosodimethylamine (NDMA), a probable human carcinogen previously found in certain recalled valsartan products, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA. FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The [combined headspace method \(/media/117843/download\)](/media/117843/download) and the [combined direct injection method \(/media/117807/download\)](/media/117807/download) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers to ensure their products are not at risk for NDMA or NDEA formation. The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

For additional information about ARB products, see:

- [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download)
- [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download)

10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [10/24/2018] FDA continues to evaluate valsartan-containing products and other angiotensin II receptor blockers (ARBs), and has updated [the list of products included in the recall \(/media/118231/download\)](/media/118231/download) to add one additional lot of RemedyRepack.

10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method

Update [10/16/2018] FDA is posting a gas chromatography-tandem mass spectrometry (GC-MS/MS) method (</media/117807/download>), utilizing liquid injection for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

This method provides an additional option for regulators and industry to detect NDMA and NDEA impurities. This method can be used alone or in combination with the combined gas chromatography-mass spectrometry (GC/MS) headspace method (</media/117843/download>), the agency recently posted. Like the previously posted methods, this method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA

Update [10/11/2018]] FDA is posting a redeveloped combined gas chromatography-mass spectrometry (GC/MS) headspace (</media/117843/download>) method for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

FDA previously posted a GC/MS method for detection of NDMA in valsartan products. Upon detection of NDEA in valsartan products manufactured by Zhejiang Huahai Pharmaceuticals, FDA redeveloped the testing method so that it can be used to detect and quantify levels of both NDMA and NDEA. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

FDA is also working on a GC/MS direct injection method for detection of NDMA and NDEA. We will post the method when it is available. This will provide an additional option for regulators and industry to use to detect both impurities.

10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products

Update [10/5/2018] FDA posted laboratory test results showing NDMA levels in recalled valsartan products. FDA will also post [test results \(/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products\)](/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) and an assessment of the cancer risk from NDEA when they are available.

9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert

Update [9/28/2018] FDA placed Zhejiang Huahai Pharmaceuticals on [import alert \(https://www.accessdata.fda.gov/cms_ia/importalert_189.html\)](https://www.accessdata.fda.gov/cms_ia/importalert_189.html) on September 28, 2018, to protect U.S. patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent [inspection \(/media/117875/download\)](/media/117875/download) at ZHP's facility.

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [9/24/2018] FDA has updated the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) with five Teva products that were not previously on either list.

9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products

Go to [Press Release \(/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional\)](/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional).

8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current\)](/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current).

8/24/2018: UPDATE - FDA updates recall lists

Update [8/24/2018] Torrent Pharmaceuticals Limited is expanding its voluntary [recall](/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall) (</safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall>). FDA has updated the [list of valsartan products under recall](/media/118231/download) (</media/118231/download>).

8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [8/22/2018] Torrent Pharmaceuticals Limited is expanding its voluntary recall to all lots of unexpired valsartan-containing drug products due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals.

RemedyRepack, a repackager of Torrent's valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets, has also recalled.

FDA has updated the [list of valsartan products under recall](/media/118231) (</media/118231>) and the [list of valsartan products not under recall](/media/118232/download) (</media/118232/download>).

Additionally, FDA is releasing a gas chromatography-mass spectrometry ([GC/MS](/media/115965/download)) [headspace method](/media/115965/download) (</media/115965/download>) for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. The agency is using this method to test potential NDMA-containing APIs and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods

Update [8/20/2018] FDA is alerting health care professionals and patients that Torrent Pharmaceuticals Limited is voluntarily [recalling](/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets) (</safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets>). 14 lots of valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets. Not all Torrent valsartan products distributed in the U.S. are being recalled.

FDA recently learned Torrent used affected valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. FDA testing confirmed NDMA in some Torrent products.

To date, Torrent has not received any reports of adverse events related to this recall.

FDA has updated the [list of valsartan products under recall \(/media/118231\)](/media/118231) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) to incorporate additional repackagers of Camber's valsartan products and Torrent's recall.

NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.

**Estimated Range of Daily NDMA Consumption for certain foods
(Recommended daily food consumption rates based on [Dietary Guidelines for Americans 2015-2020](https://health.gov/dietaryguidelines/2015/guidelines/) (<https://health.gov/dietaryguidelines/2015/guidelines/>))**

- Cured meat - 0.004-0.23 micrograms¹
- Smoked meat - 0.004-1.02 micrograms¹
- Grilled meat - 0.006-0.13 micrograms¹
- Bacon - 0.07-0.09 micrograms²
 - In more ordinary terms, for example, one pound of bacon may contain 0.304-0.354 micrograms of NDMA

FDA reminds patients taking valsartan from a recalled lot that they should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. Not all valsartan products contain NDMA, so pharmacists may be able to provide a refill of valsartan medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

¹ Mavelle, T., B. Bouchikhi, and G. Debry, *The occurrence of volatile N-nitrosamines in French foodstuffs. Food Chemistry*, 1991. 42(3): p. 321-338.

² Park, J., et al., *Distribution of Seven N-Nitrosamines in Food. Toxicol Res*, 2015. 31(3): p. 279-288.

8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [8/9/2018] FDA has updated the [list of valsartan products under recall \(/media/118231\)](/media/118231) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) to incorporate recalls of valsartan-containing products manufactured by Hetero Labs Limited, in India, labeled as Camber Pharmaceuticals Inc. Not all Camber valsartan products distributed in the U.S. are being recalled.

Camber Pharmaceuticals is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg\)](/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg) certain valsartan tablets because they contain the impurity N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient (API). Hetero Labs manufactures the API for the Camber products using a process similar to Zhejiang Huahai Pharmaceuticals.

Test results from Hetero Labs show the amount of NDMA found in its valsartan API exceeds acceptable levels; although it is generally lower than the amount discovered in the API manufactured by Zhejiang.

FDA is testing samples of valsartan API and finished products to confirm the extent and amount of NDMA and help inform the ongoing investigation. The agency has also contacted other manufacturers of valsartan API to determine if their manufacturing processes are at risk for the formation of NDMA, and is working with them to ensure NDMA is not present in future valsartan API.

Valsartan is an angiotensin II receptor blocker (ARB), and FDA is investigating whether other types of ARBs are at risk for the presence of NDMA.

Recalled valsartan products labeled as Camber may be repackaged by other companies. FDA will provide updates as more information becomes available.

8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities

Update [8/2/2018] FDA continues to evaluate valsartan-containing products and has updated the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download). In addition to updating the lists, FDA revised information related to A-S Medication on the list of products included in the recall. The agency will continue to provide information when it becomes available.

FDA is working with drug manufacturers to ensure future valsartan active pharmaceutical ingredients (APIs) are not at risk of NDMA formation. The agency reminds manufacturers to thoroughly evaluate their API manufacturing processes, and changes to those processes,

to detect any unsafe impurities. If a manufacturer detects new or higher levels of impurity, they should take action to prevent changes to the product's safety profile.

7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [7/27/2018] FDA is updating health care professionals and patients after discovering that several additional companies that repackage drug products are also recalling valsartan-containing products.

FDA has product recall information from three additional repackagers of valsartan-containing products made by Teva Pharmaceuticals and Princeton Pharmaceuticals Inc. – labeled as A-S Medication Solutions LLC, AvKARE and RemedyRepack – and the agency has added them to the recalled products list. Two of these companies, A-S Medication and RemedyRepack, may also distribute valsartan products not affected by the recall. The agency is confirming this information and will provide an update once it is available.

The following additional repackagers are recalling or are expected to recall valsartan-containing products. FDA is working to gather product recall information from these companies and has removed them from the list of products that are not impacted by this recall:

- Bryant Ranch Prepack Inc.
- H. J. Harkins Company Inc. (*this company was not originally included on either list*)
- Lake Erie Medical, doing business as Quality Care Products LLC
- NuCare Pharmaceuticals Inc.
- Northwind Pharmaceuticals
- Proficient Rx

It is possible that not all valsartan-containing products repackaged by these companies are impacted by the recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download) as more information becomes available.

7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.

Update [7/27/2018] On July 13th, FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA). Valsartan is a medication commonly used to treat high blood pressure and heart failure.

NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches. Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen (https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf)—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods¹. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion². It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.

The amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. The agency wanted to put some context around the actual potential risk posed to patients who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, some levels of the impurity may have been in the valsartan-containing products for as long as four years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people. This assessment led to FDA's decision to have these batches recalled.

Patients taking valsartan from a recalled batch should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. It is important to know that not all valsartan products contained NDMA, so pharmacists may be able to provide a refill of valsartan medication from batches that are not affected by the recall, or doctors may prescribe a different medication that treats the same indications.

FDA continues to evaluate the safety of valsartan-containing products and will update the list of products included in the recall (</media/118231/download>) and the list of products not included in the recall (</media/118232/download>) as more information becomes available. If you are taking a valsartan product, be sure to check to back as the lists may change.

¹ From Toxnet: <https://toxnet.nlm.nih.gov/> (<https://toxnet.nlm.nih.gov/>).

Average Daily Intake: WATER: (assume 3 to 6 ng N-nitrosodimethylamine/l)(1) 6 to 12 ng; direct intake from drinking water is probably much less than 1 ug/day(2). FOOD: (assume <0.1 to="" 84="" ug/kg)(4)="" ><0.16 to="" 134="" >

[(1) Kimoto WI et al; Water Res 15: 1099-1106 (1981) (2) USEPA; Ambient Water Quality Criteria Doc: Nitrosamines p.C-14 (1980) EPA 440/5-80-064 (4) IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 17: 125-76 (1978)]

² The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

([http://wcms-internet.fda.gov/files/drugs/published/M7-R1-](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)

[AssessmentAndControlOfDNA-Reactive-Mutagenic-](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)

[ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)

([http://wcms-internet.fda.gov/files/drugs/published/M7-R1-](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)

[AssessmentAndControlOfDNA-Reactive-Mutagenic-](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)

[ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf)))

7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall

Update [7/24/2018] FDA is updating health care professionals and consumers on the agency's progress in responding to the ongoing recalls of valsartan, which is used to treat high blood pressure and heart failure, due to the presence of NDMA. The agency has posted a [list of valsartan-containing products not impacted \(/media/118232/download\)](/media/118232/download) by this recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download) as more information becomes available.

Manufacturers of these products often produce multiple dosage strengths, however not all of them are being recalled. FDA recommends health care professionals and patients carefully check these lists. Health care professionals and patients should check this statement frequently for any updates.

FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death.

Consumers and health care professionals should continue to report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>).
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178.

7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls

[7/18/2018] The U.S. Food and Drug Administration is updating health care professionals and consumers following a recent FDA press release (/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity) about voluntary recalls of several drug products containing the active pharmaceutical ingredient (API) valsartan. Valsartan is used to treat high blood pressure and heart failure. Not all products containing valsartan are being recalled, and this update will clarify which valsartan-containing products are being recalled.

The recalled products contain an impurity, N-nitrosodimethylamine (NDMA), in the API manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

The investigation into valsartan-containing products is ongoing, and the following list may change. We will update this statement as we have more information.

There are currently three voluntary recalls related to the NDMA impurity detected in the valsartan API:

- **Teva Pharmaceuticals USA labeled as Major Pharmaceuticals** — recall is at the **retail level** because these products are only used in facilities where they are directly administered to patients by health care professionals: Valsartan 80 mg and 160 mg products;

- **Princeton Pharmaceuticals Inc. labeled as Solco Healthcare LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products; and
- **Teva Pharmaceuticals labeled as Actavis LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products.

Detailed list of products included in the recall (/media/118231/download). (PDF - 87 KB)

What should patients know:

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Not all valsartan-containing medications are affected and being recalled.
- If you are taking any medication containing valsartan, compare the information on your prescription bottle with the information in this list (/about-fda/page-not-found) (company, National Drug Code, lot number) to determine if your current medicine has been recalled. If you are not certain, contact your pharmacist.
- If you have medicine included in the recall, contact your pharmacist. The pharmacist may be able to provide you with valsartan made by another company. If not, contact your doctor immediately to discuss other treatment options.

What health care professionals should know:

- FDA has determined the recalled valsartan products pose an unnecessary risk to patients. Therefore, FDA recommends patients use valsartan-containing medicines made by other companies or consider other available treatment options for the patient's medical condition.
- If you have medication samples from these companies, quarantine the products and do not provide them to patients.

Consumers and health care professionals should report any adverse reactions with valsartan-containing products, to the FDA's MedWatch program (<https://www.fda.gov/safety/medwatch/>) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>).

- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178.

7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

Go to [Press Release \(/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity\)](/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity).

FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities

The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- [Combined headspace method \(/media/117843/download\)](/media/117843/download): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- [Combined direct injection method \(/media/117807/download\)](/media/117807/download): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- [Direct injection GC-MS method \(/media/123409/download\)](/media/123409/download): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- [Headspace GC-MS method \(/media/124025/download\)](/media/124025/download): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- [LC-HRMS method \(/media/125478/download\)](/media/125478/download): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- [RapidFire-MS/MS method \(/media/125477/download\)](/media/125477/download): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published [methods to detect NDMA and NDEA \(https://www.edqm.eu/en/ad-hoc-](https://www.edqm.eu/en/ad-hoc-)

projects-omcl-network). <http://www.fda.gov/about-fda/website-policies/website-disclaimer>). FDA has not validated EDQM's methods.

Resources for You

- [Search ARBs Recalls List \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)
- [Recalls of ARBs including Valsartan, Losartan and Irbesartan \(/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)
- [Nitrosamine Impurities in Medications \(/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications\)](/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)

Exhibit 4

N-Nitrosodimethylamine

CASRN 62-75-9 | DTXSID7021029

- [IRIS Summary \(PDF\)](#). (11 pp, 105 K)

[Key IRIS
Values](#)

[Other EPA
Information](#)

Noncancer Assessment

[Reference Dose for Oral Exposure \(RfD\) \(PDF\)](#). (11 pp, 105 K)

Not assessed under the IRIS Program.

Last Updated:

[Reference Concentration for Inhalation Exposure \(RfC\) \(PDF\)](#).

(11 pp, 105 K)

Not assessed under the IRIS Program.

Cancer Assessment

[Weight of Evidence for Cancer \(PDF\)](#). (11 pp, 105 K)

Last Updated: 01/31/1987

WOE Characterization	Framework for WOE Characterization
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodents and nonrodent mammals exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF) (11 pp, 105 K)

Oral Slope Factor: 5.1×10^1 per mg/kg-day

Drinking Water Unit Risk: 1.4×10^{-3} per $\mu\text{g/L}$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF) (11 pp, 105 K)

Inhalation Unit Risk: 1.4×10^{-2} per $\mu\text{g/m}^3$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

You will need Adobe Reader to view some of the files on this page. See [EPA's PDF page](#) to learn more.

[Contact Us](#) to ask a question, provide feedback or report a problem.

Related Links

- [EPA Chemicals Dashboard - N-Nitrosodimethylamine](#)
- [eChemPortal - Nitrosodimethylamine](#)

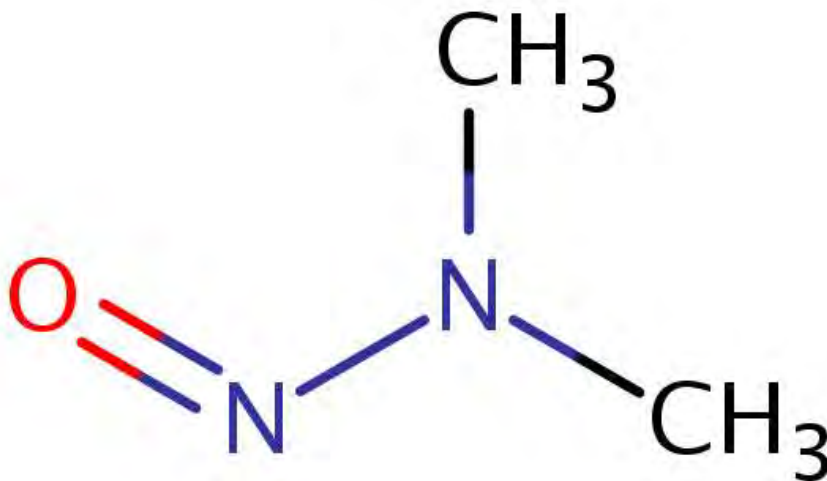
Tumor Sites



Hepatic

Chemical Structure for

N-Nitrosodimethylamine



Synonyms

- Dimethylamine, n-nitroso
- Dimethylnitrosamin
- Dimethylnitrosamine
- Dmna: dmn
- Methylamine, n-nitrosodi-

[more synonyms](#)

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit 5

N-Nitrosodiethylamine

CASRN 55-18-5 | DTXSID2021028

- [IRIS Summary \(PDF\)](#). (11 pp, 106 K)

[Key IRIS
Values](#)

[Other EPA
Information](#)

Noncancer Assessment

[Reference Dose for Oral Exposure \(RfD\) \(PDF\)](#). (11 pp, 106 K)

Not assessed under the IRIS Program.

Last Updated:

[Reference Concentration for Inhalation Exposure \(RfC\) \(PDF\)](#).

(11 pp, 106 K)

Not assessed under the IRIS Program.

Cancer Assessment

[Weight of Evidence for Cancer \(PDF\)](#). (11 pp, 106 K)

Last Updated: 01/31/1987

WOE Characterization	Framework for WOE Characterization
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodent and nonrodent species exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure (PDF) (11 pp, 106 K)

Oral Slope Factor: 1.5×10^2 per mg/kg-day

Drinking Water Unit Risk: 4.3×10^{-3} per $\mu\text{g/L}$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure (PDF) (11 pp, 106 K)

Inhalation Unit Risk: 4.3×10^{-2} per $\mu\text{g/m}^3$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

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Related Links

- [EPA Chemicals Dashboard - N-Nitrosodiethylamine](#)
- [eChemPortal - Nitrosodiethylamine](#)

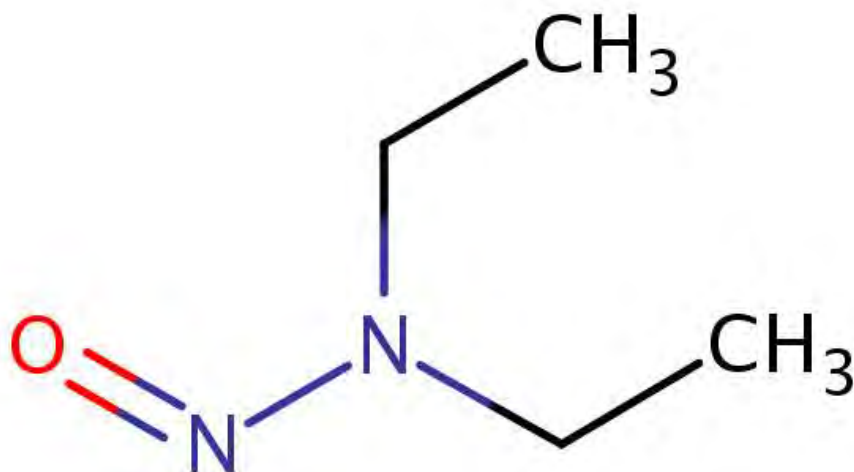
Tumor Sites



Hepatic

Chemical Structure for

N-Nitrosodiethylamine



Synonyms

- Dana: den
- Dena
- Diaethylnitrosamin
- Diethylamine, n-nitroso
- Diethylnitrosamine

[more synonyms](#)

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit 6

Welcome



Empowering a healthy tomorrow

SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

By: Edmond Biba
Senior Scientific Liaison,
Science – General Chapters

Webinar
July 28, 2020



Background

Introduction



- ▶ Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- ▶ However, their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens.
- ▶ They are part of a group of high potency mutagenic carcinogens referred to as the “cohort of concern” in ICH M7. This “cohort of concern” comprises aflatoxin-like, N-nitroso- (functional group of nitrosamines), and alkyl-azoxy compounds

Exhibit 7

Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan

Jinsheng LIN

To: Jucai GE, Tianpei HUANG, Wangwei CHEN, Wenquan ZHU, Wenbin CHEN, Mr. Li, Peng DONG, Lihong LIN, Yanfeng LIU, Peng WANG, Wenling ZHANG
07/27/2017 Detailed Information

Valsartan Impurity K.pdf (846 KB)

Ms. Ge:

According to the results of our telephone communication with the Technology Department of Chuannan Plant 1 today, due to the incomplete quenching of sodium azide caused by the separate treatment of irbesartan sodium azide wastewater, there is the frequent occurrence of muffled explosion in the production process, so the Technology Department carried out the technical improvement by which the sodium azide quenching takes place in the unstratified step in the crude irbesartan process. However, after the improvement, there is an unknown impurity of about 0.544% at 26 minutes in the crude irbesartan, and it is the largest impurity in the irbesartan crude product.

[REDACTED]

[REDACTED]

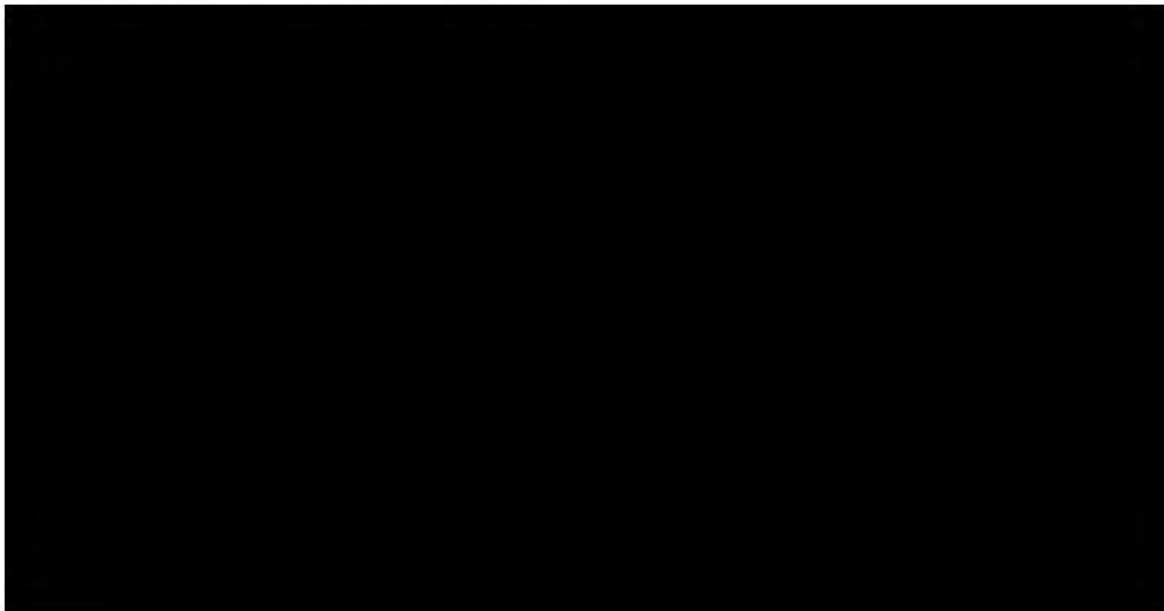
[REDACTED]

Min Li

ZHP-296

4/20/2021

Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic. Its possible formation route is shown as follows:



In order to further verify the structure of the impurity and its formation mechanism, we plan to simulate the quenching conditions and use the finished Irbesartan product to react with NaNO_2 and HCl to monitor the impurity produced by the reaction, and then separate it for NMR for final structural verification, while simultaneously carrying out the confirmation of the impurity by multi-stage MS.

If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process.

I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Ltd. they proposed that the use of NaNO_2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude Valsartan in their LC-MS test and detected this impurity. This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.

Jinsheng LIN

CEMAT

2017/07/27

Exhibit 10

FDA STATEMENT

FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues

For Immediate Release:

January 25, 2019

Statement From:

Scott Gottlieb, M.D.

Last summer, the FDA learned and reported that some generic versions of the angiotensin II receptor blocker (ARB) medicines contain nitrosamine impurities that don't meet the agency's safety standards. ARBs, including valsartan, irbesartan, losartan and others, are a class of medicines used to treat high blood pressure and heart failure. Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), are probable human carcinogens. These two substances are known environmental contaminants and found in water and foods, including meats, dairy products and vegetables. But their presence in drug products is not acceptable.

We were deeply concerned when we learned about the presence of these impurities. We immediately undertook a major operation to investigate and to identify the root causes for the presence of these impurities in some ARB drugs, and to work with companies to address the risks that the impurities pose to patients.

Our analysis of NDMA found that the risk to patients based on the maximum possible exposure appears to be small. That doesn't diminish our concern and our determination to find out how these impurities occurred in the first instance. We're committed to implementing measures to prevent these impurities from occurring in the manufacturing process in the future. Our ultimate goal is to ensure that these impurities are not present in finished drug products, or their components (including active pharmaceutical ingredients, or API).

There remains a great deal of public interest in this matter. Today, we want to provide an update on this ongoing investigation and outline the steps we've taken to identify the root causes of the nitrosamine impurities and to prevent a recurrence of this episode in the future. This continues to be an exhaustive effort led by a multidisciplinary team of chemists, toxicologists, physicians, pharmacists, communication specialists, investigators and analytical laboratory staff from across the FDA and in collaboration with global regulators.

Exhibit
0010
Hecht

While we're still investigating the root causes of the impurities, our ongoing effort has determined that the impurities may be generated when specific chemicals and reaction conditions are present in the manufacturing process of the drug's API, and may also result from the reuse of materials, such as solvents.

This issue surfaced in the summer of 2018, when the FDA was informed that API manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd. (ZHP), in Linhai, Taizhou Zhejiang China for some generic valsartan-containing medicines contained NDMA, posing a potential safety concern.

Since then, the FDA and additional manufacturers of other ARB medicines have identified more cases of NDMA impurities, as well as NDEA impurities. We've placed a ZHP facility on import alert to stop all its API and finished drugs made using ZHP's API from legally entering the U.S. We also issued them a warning letter outlining several manufacturing violations, including impurity control, change control and cross contamination from one manufacturing process line to another. It's unlikely that the subtle problems causing these impurities could have been found on a routine current good manufacturing practice (CGMP) inspection. Nonetheless, our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise.

We've also worked with manufacturers of all ARB medicines to recall any product that poses a risk to patients. Because of the way API is distributed in the supply chain, one source of contaminated API can impact multiple products. As part of this continuing process, last week, we alerted patients and health care professionals to a voluntary recall of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Princeton Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of NDEA in the irbesartan API manufactured by ZHP. We will continue to keep the public updated via our [website \(/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications\)](/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications) of all products being recalled. While we acted aggressively to address the issue once we became aware of it, we must also answer the critical question of, why weren't these impurities detected earlier? We've also been asked whether the FDA could have prevented this from occurring if we had done something differently during surveillance inspections in the preceding years.

We want to lay out the many steps we take to mitigate these kinds of risks.

We engage experts in organic chemistry to detect circumstances that can create the risk for these kinds of impurities to be introduced as a by-product of the manufacturing process or changes made in that process. We also work with international regulators to create standards for mitigating the risk of this type of chemical impurity, known as a "genotoxic" impurity. These chemicals, including NDMA and NDEA, are of special concern to global regulators because, unlike most impurities in drugs, they have the potential to cause harm at very low levels. That's why we have robust policies and procedures in place to guard against these risks.

In March 2018, the FDA issued a [guidance \(/media/93672/download\)](/media/93672/download) for manufacturers that lays out risk assessments that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally-harmonized guidance that regulators and industry have agreed to. The FDA reviews information on impurity testing in product applications and when inspecting facilities. Manufacturers must test for known impurities during their manufacturing processes.

We review information about potential impurities that can occur during manufacturing in applications, including requests that sponsors submit to change some aspects of the manufacturing process, which could create new risks. Specifically, our chemists review applications and referenced information to look for steps and changes where risks could be introduced. To implement a risk assessment for any genotoxic impurity, there must be recognition that it can occur in a product's manufacturing. The guidance lays out the conditions under which these risks can occur and steps that manufacturers should take to test for these potential impurities. Now that we've uncovered the risk of nitrosamine impurities in the manufacturing steps involved in ARBs, we'll incorporate the findings into ongoing policy development.

In addition to our policy work, the FDA inspects manufacturing facilities worldwide. Generally during CGMP inspections, we review the records that manufacturers must maintain regarding required impurity testing. However, the impact of this record review depends on manufacturers conducting appropriate tests that are capable of detecting the impurity. Tests are selected based on assessments of what impurities may develop as a result of the manufacturing process. In other words, it generally needs to be recognized that there's a risk of an impurity occurring as a result of a manufacturing process to know the impurity should be tested for.

Our investigation into ZHP's process identified that a change made to the manufacturing process likely led to this impurity, and that the impurity went undetected by global regulators, including the FDA, for a period of time. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA or NDEA could form during this particular manufacturing process. This is troubling to us and we know it's troubling to the public. This concern is appropriate. Among other steps, we need to take actions that would prevent a similar situation from occurring. We are making important strides at understanding how these impurities occurred, mitigating the risk to patients and learning what steps need to be taken to prevent this from occurring again in the future.

One challenge we've faced is that NDMA's properties make it hard to detect in standard laboratory testing – the kind of testing results that are reviewed during a surveillance inspection. In St. Louis, the FDA maintains one of the most advanced pharmaceutical laboratories of any regulatory agency in the world. As soon as we became aware of the presence of nitrosamine impurities in certain ARB medicines, we began collecting samples of all ARB API and medicines marketed in the U.S. to test these products specifically for NDMA. More testing found NDEA, also a probable human carcinogen, in other valsartan products and other ARBs from different manufacturers.

During this time, our scientists have developed and refined novel and sophisticated testing methods specifically designed to detect and quantify the NDMA and NDEA in all ARB medicines. We've shared these tests on our website to help manufacturers and other regulators evaluate these products as well. To determine if ARB medicines contain these impurities, FDA scientists developed three testing methods. These include the [GC/MS headspace method \(/media/115965/download\)](/media/115965/download), the [combined headspace method \(/media/115965/download\)](/media/115965/download), and the [combined direct injection method \(Combined N-Nitrosodimethylamine \(NDMA\) and N-Nitrosodiethylamine \(NDEA\)\)](#). These testing methods can be used for evaluating both drug substances (API) and finished drug products.

Medicines that contain NDMA or NDEA above [certain limits \(/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan\)](/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan) (see 12/19/2018 update) pose an unacceptable risk to patients, and ARBs that contain impurities above these

levels are being recalled. We've also posted lists of valsartan (</media/118231/download>), losartan (</media/119422/download>), and irbesartan (</media/118233/download>) products affected by the recalls. We'll continue to update these lists as new information develops. And we'll continue to work with manufacturers to ensure all affected products are quickly removed from market. We're also working with API makers to ensure that they fix their processes and cease distribution of affected API.

We know patients rely on these medicines. Part of our work throughout this process has been to mitigate and prevent shortages, where possible. Currently, valsartan products are in shortage, and we know that other types of products may fall into shortage soon. That's why the agency has also evaluated safety data for NDMA and NDEA to determine interim acceptable intake levels for these impurities in the ARB class of medicines. While consumers should limit exposure to NDMA and NDEA, these impurities exist in other ingested products, such as some charcoal grilled food items. And so, our goal is to balance the risk of patients ingesting low levels of the impurities (below the interim acceptable levels) for a short period of time with the risk that there is a shortage of certain ARBs, which may impact patients' ability to access the medicine they need. We remind patients taking these medications or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

Overall, the risk to individual patients remains very small, although this doesn't diminish the significance of this episode or our concerns. FDA scientists estimate that if 8,000 people took the highest daily valsartan dose (320 mg) that contained NDMA, for four years (the time we think the affected products had been on the U.S. market), there may be one additional case of cancer beyond the average cancer rate among those 8,000 Americans. The vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario. Since not all ARBs are affected, it's very likely that a patient taking an ARB for four years would not have always received one of the affected products. We're still seeking to similarly quantify the risk from NDEA and plan to communicate our findings as soon as possible.

Now that these risks are identified, we're applying what we've learned to the evaluation of similar manufacturing processes where we now know these risks could arise. As part of this process, the FDA has identified specific factors in manufacturing processes that may contribute to the formation and presence of NDMA and NDEA. Through our investigation, we're working to ensure that other manufacturing conditions don't contribute to NDMA, NDEA, or related impurities in finished drug products. We'll use the information we've learned about these impurities when reviewing applications, assessing manufacturing changes and conducting inspections. Now that they are aware that certain conditions result in the formation of nitrosamines, manufacturers using processes at risk for these impurities are expected to test for them to ensure that active ingredients and finished products are free of detectable levels of a nitrosamine impurities resulting in drug products that that are safe for patients.

While the total exposure to these impurities for most patients was small, we are deeply concerned that patients were exposed to this impurity in the first place and that the presence of nitrosamines went undetected for a period of time. The potential for the development of genotoxic impurities during manufacturing processes is an area of intense focus. We'll continue to improve our science and standards for detecting and preventing these risks.

We'll also continue to keep the public informed on our [website \(FDA updates on angiotensin II receptor blocker \(ARB\) recalls including valsartan, losartan and irbesartan\)](#), which contains most current information. Patients and providers can also send email to druginfo@fda.hhs.gov ([/about-fda/page-not-found](#)) or call 855-543-3784. We're also encouraging submission of any information related to potential side effects to our [MedWatch program](#) ([http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/#!/--\\$wcmUrl\('nodelink','2237'\)--](http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/#!/--$wcmUrl('nodelink','2237')--))).

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Inquiries

Media:

✉ [Sarah Peddicord \(mailto:sarah.peddicord@fda.hhs.gov\)](mailto:sarah.peddicord@fda.hhs.gov)

☎ 301-796-2805

Consumer:

☎ 888-INFO-FDA

➡ [More Press Announcements \(/news-events/newsroom/press-announcements\)](#)

Exhibit 11



U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

Warning Letter: 320-19-04

November 29, 2018

Mr. Jun Du
Executive Vice President
Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai Fifth Avenue, Linhai, Taizhou Zhejiang 317016
CHINA

Dear Mr. Du:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, from July 23 to August 3, 2018.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your August 26, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Valsartan API

Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DC_E-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing

process (referred to as the ZnCl_2 process in your investigation) was impacted by the presence of NDMA.

However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the triethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:

- To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including potable water.
- To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending, solvent recovery and re-use, shared production lines, and cleaning procedures.
- To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates (C20213-17-339 and C20213-17-340) failed testing for an unknown impurity (specification $\leq 0.5\%$) with results of 0.56% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your ZnCl_2 process, with DMF in 2012 (C5355-12-001, C5355-12-002, and C5355-12-003) show at least one unidentified peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

In response to this letter:

- Submit risk assessments for all APIs and intermediates manufactured at your facility for the potential presence of mutagenic impurities.
- Provide an update on investigations and CAPA plans initiated to address the presence of NDMA and other potential mutagenic impurities in all APIs manufactured at your firm.
- Provide a thorough, independent assessment of your overall system for investigating deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications or appropriate manufacturing standards.
- Provide test results for all angiotensin II receptor blockers (ARBs) and intermediates for the presence of NDMA, N-Nitrosodiethylamine (NDEA), and other potentially mutagenic impurities.

Levetiracetam API

Your firm received a customer complaint on September 13, 2016, concerning levetiracetam API batches (C5152-16-243 and C5152-16-254) that exceeded the specification for ethyl carbamate (≤ 0.24 ppm). Ethyl carbamate has been classified as a probable human carcinogen. Your customer's test results conflicted with your ethyl carbamate test results, which showed the two batches meeting the specification upon release. Your complaint investigation (CC-16008) identified no clear laboratory error, and no anomalies were detected during the production of the batches. Your investigation failed to evaluate other levetiracetam API batches to determine if the presence of excess ethyl carbamate was an adverse trend. For example, levetiracetam batches C5152-16-244, C5152-16-250, and C5152-16-251 were OOS for ethyl carbamate because of production errors; however, they were not discussed in your complaint investigation.

Your response states that levetiracetam API batches C5152-16-243 and C5152-16-254 were returned, reprocessed, and released to customers in non-U.S. markets.

Your response also states that in August 2017 you implemented a new ethyl carbamate test method that uses a triple quadrupole LC-MS/MS method, to replace the single quadrupole LC-MS method that was prone to erroneous OOS results. You failed to verify the reliability of the ethyl carbamate results for all levetiracetam API batches (including levetiracetam batch C5152-16-254) originally released using your single quadrupole LC-MS method, which you indicated was inferior to your updated method.

In response to this letter, provide:

- A risk assessment for all levetiracetam API batches manufactured within expiry.
- A revised complaint handling procedure and details of any further controls your facility has implemented to ensure that all complaints are adequately documented and thoroughly investigated.

- Procedures for accepting and reprocessing returned drugs.
- Results of ethyl carbamate testing of all levetiracetam API batches released to the U.S. market using your updated triple quadrupole LC-MS/MS ethyl carbamate test method.

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.

Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* for approaches that FDA considers appropriate for evaluating mutagenic impurities, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>.

In response to this letter, provide:

- Detailed revised change management procedures describing how your firm will assess and control all impurities, including mutagenic impurities, in API and intermediates manufactured at your facility.

- Detailed procedures describing how your firm establishes impurity profiles for products manufactured at your firm. These procedures should contain instructions for comparing at appropriate intervals against the impurity profile in the regulatory submission, or for comparing against historical data, to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- A retrospective analysis of other API and intermediates manufactured at your firm to determine if they were adequately evaluated for anticipated and unanticipated impurities, including potentially mutagenic impurities.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Quality Systems Guidance

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf>; *Q9 Quality Risk Management*, at <https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>; and *Q10 Pharmaceutical Quality System*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf>.

Additional API CGMP guidance

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API, at <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what

actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

FDA placed your firm on Import Alert 66-40 on September 28, 2018.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Rory K. Geyer
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003885745.

Sincerely,



Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Exhibit 13

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE**

**IN RE: VALSARTAN, LOSARTAN,
AND IRBESARTAN PRODUCTS
LIABILITY LITIGATION**

MDL No. 2875

Honorable Robert B. Kugler,
District Court Judge

This Document Relates to All Actions

STIPULATION OF ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Pursuant to Special Master Report and Order No. 56, in exchange for Plaintiffs' agreement not to further examine a witness at deposition regarding the statements identified herein, Defendant Zhejiang Huahai Pharmaceutical Co., Ltd. ("ZHP") hereby stipulates as follows:

1. ZHP states that there are no health benefits associated with the presence of NDMA or NDEA in valsartan.
2. ZHP states that the publication *Purification of Laboratory Chemicals* (4th ed.) by W.L.F. Armarego and D.D. Perrin, which was first published in 1996 and documented scientific knowledge at that time, states on page 192 that DMF

“[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide.”

3. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:
 - a. ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.
 - b. The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.
 - c. Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.
 - d. ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. ZHP is not saying that it was not possible to know that DMF could degrade.
 - e. ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

4. With regard to the Change Request Form identified as Exhibit 195 to the March 28/29, 2021 deposition of Peng Dong (copy of Exhibit attached hereto as Exhibit 1), ZHP states the following:

- a. The “Explanation Section” in Section 2 of the Change Request form on the page bearing Bates number ZHP01843067 provides a summary of the explanation for why the process change from the triethylamine hydrochloride process to the zinc chloride process was undertaken.
- b. One of the reasons for the quality review described in Section 3 of the Change Request Form on the page bearing Bates number ZHP01843069 was to identify impurities due to the new process.
- c. Section 3 of the Change Request Form on the page bearing Bates number ZHP01843070 provided that if this change was against cGMP code, it was supposed to be rejected.

Dated: May 13, 2022	<u>/s/ Richard T. Bernardo</u> Richard T. Bernardo SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP One Manhattan West New York, NY 10001-8602 richard.bernardo@skadden.com Jessica D. Miller SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP 1440 New York Avenue, N.W. Washington, D.C. 20005 jessica.miller@skadden.com Counsel for Defendant
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Exhibit 15

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF NEW JERSEY
3 CAMDEN VICINAGE

4 -----

5 IN RE: VALSARTAN, MDL NO. 2875
6 LOSARTAN, AND
7 IRBESARTAN PRODUCTS CIVIL ACTION NO.
8 LIABILITY LITIGATION 19-2875
9 (RBK/JS)

10 -----

11 THIS DOCUMENT APPLIES HONORABLE
12 TO ALL CASES ROBERT B. KUGLER

13 -----

14 - CONFIDENTIAL INFORMATION -

15 SUBJECT TO PROTECTIVE ORDER

16

17 REMOTE VIDEOTAPED EXPERT DEPOSITION OF

18 FENGtian XUE, PHD

19 Friday, February 3, 2023

20 10:04 a.m. Eastern Time

21

22 Stenographically Reported by:

23 Denise Dobner Vickery, CRR, RMR,

24 Court Reporter, Notary Public JOB NO.: 329090

Page 2	Page 4
<p>1 REMOTE APPEARANCES VIA ZOOM:</p> <p>2</p> <p>3 Representing the Plaintiffs:</p> <p>4 MAZIE SLATER KATZ & FREEMAN, LLC</p> <p>5 BY: ADAM M. SLATER, ESQ.</p> <p>6 BY: CHRISTOPHER J. GEDDIS, ESQ.</p> <p>7 103 Eisenhower Parkway</p> <p>8 Roseland, NJ 07068</p> <p>9 973.228.9898</p> <p>10 aslater@mazieslater.com</p> <p>11 cgeddis@mazieslater.com</p> <p>12</p> <p>13 Representing the Plaintiffs:</p> <p>14 MEYER WILSON CO., LPA</p> <p>15 BY: LAYNE HILTON, ESQ.</p> <p>16 900 Camp Street, Suite 337</p> <p>17 New Orleans, LA 70130</p> <p>18 614.255.2697</p> <p>19 lhilton@meyerwilson.com</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1 REMOTE APPEARANCES VIA ZOOM: (Cont'd.)</p> <p>2</p> <p>3 Representing the Defendants Zhejiang Huahai</p> <p>4 Pharmaceutical Co., Ltd., Prinston Pharmaceutical</p> <p>5 Inc., Huahai U.S., Inc., and Solco Healthcare US,</p> <p>6 LLC:</p> <p>7 SKADDEN ARPS SLATE MEAGHER & FLOM LLP</p> <p>8 BY: RICHARD BERNARDO, ESQ.</p> <p>9 BY: JOSHUA SCHOCH, ESQ.</p> <p>10 One Manhattan West</p> <p>11 New York, NY 10001</p> <p>12 212.735.2994</p> <p>13 Richard.Bernardo@skadden.com</p> <p>14 Joshua.Schoch@skadden.com</p> <p>15</p> <p>16 For Defendants Teva Pharmaceutical Industries,</p> <p>17 Ltd., Teva Pharmaceuticals USA, Inc., Actavis</p> <p>18 LLC, and Actavis Pharma, Inc.:</p> <p>19 GREENBERG TRAURIG LLP</p> <p>20 BY: BRIAN RUBENSTEIN, ESQ.</p> <p>21 1717 Arch Street, Suite 400</p> <p>22 Philadelphia, PA 19103</p> <p>23 215.988.7864</p> <p>24 rubensteinb@gtlaw.com</p>
Page 3	Page 5
<p>1 REMOTE APPEARANCES VIA ZOOM: (Cont'd.)</p> <p>2</p> <p>3 Representing the Plaintiffs:</p> <p>4 RIVERO MESTRE LLP</p> <p>5 BY: ZALMAN KASS, ESQ.</p> <p>6 BY: JORGE A. MESTRE, ESQ.</p> <p>7 2525 Ponce de Leon Boulevard, Suite 1000</p> <p>8 Miami, FL 33134</p> <p>9 786.746.8213</p> <p>10 zkass@riveromestre.com</p> <p>11 jmestre@riveromestre.com</p> <p>12</p> <p>13</p> <p>14 Representing the Plaintiffs:</p> <p>15 MARTIN HARDING & MAZZOTTI LLP</p> <p>16 BY: ROSEMARIE RIDDELL BOGDAN, ESQ.</p> <p>17 1 Wall Street</p> <p>18 Albany, NY 12205</p> <p>19 518.724.2207</p> <p>20 Rosemarie.Bogdan@1800LAW1010.com</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1 REMOTE APPEARANCES VIA ZOOM: (Cont'd.)</p> <p>2</p> <p>3 Representing the Defendant Sciegen</p> <p>4 Pharmaceutical:</p> <p>5 HINSHAW & CULBERTSON LLP</p> <p>6 BY: GEOFFREY M. COAN, ESQ.</p> <p>7 53 State Street, 27th Floor</p> <p>8 Boston, MA 02109</p> <p>9 617.213.7045</p> <p>10 GCoan@hinshawlaw.com</p> <p>11</p> <p>12 Representing the Defendant Humana:</p> <p>13 FALKENBERG IVES LLP</p> <p>14 BY: KRISTIN B. IVES, ESQ.</p> <p>15 230 West Monroe Street, Suite 2220</p> <p>16 Chicago, IL 60606</p> <p>17 312.566.4800</p> <p>18 Kbi@falkenbergives.com</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>

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<p>1 REMOTE APPEARANCES VIA ZOOM: (Cont'd.)</p> <p>2</p> <p>3 Representing the Defendant Mylan Pharmaceuticals,</p> <p>4 Inc.:</p> <p>5 PIETRAGALLO GORDON ALFANO</p> <p>6 BOSICK & RASPANTI, LLP</p> <p>7 BY: FRANK H. STOY, ESQ.</p> <p>8 One Oxford Centre</p> <p>9 Pittsburgh, PA 15219</p> <p>10 412.263.1840</p> <p>11 fhs@pietragallos.com</p> <p>12</p> <p>13 Representing the Defendants Hetero Labs Limited</p> <p>14 and Hetero Drugs, Limited:</p> <p>15 HILL WALLACK LLP</p> <p>16 BY: WILLIAM P. MURTHA, JR., ESQ.</p> <p>17 2 Bridge Avenue, Suite 211</p> <p>18 Red Bank, NJ 07701</p> <p>19 732.924.8171</p> <p>20 wmurtha@hillwallack.com</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1 INDEX</p> <p>2 EXAMINATION OF FENGtian XUE, PHD PAGE</p> <p>3 BY MR. SLATER 13</p> <p>4 AFTERNOON SESSION 164</p> <p>5 BY MR. BERNARDO 400</p> <p>6</p> <p>7</p> <p>8 DEPOSITION EXHIBITS</p> <p>9 NUMBER DESCRIPTION PAGE</p> <p>10 Exhibit 1 Defendants' Responses and 16</p> <p>11 Objections To Plaintiffs' Notice</p> <p>12 To Take Videotaped Deposition</p> <p>13 Exhibit 2 Expert Report of Fengtian Xue, 18</p> <p>14 Ph.D., December 22, 2022</p> <p>15 Exhibit 3 Supplemental Expert Report of 28</p> <p>16 Fengtian Xue, Ph.D.,</p> <p>17 January 30, 2023</p> <p>18 Exhibit 4 Exhibit A - Amended and 31</p> <p>19 Supplemental List of Materials</p> <p>20 Reviewed and Considered</p> <p>21 Exhibit 5 Deviation regarding unknown 55</p> <p>22 Impurity (genotoxicity) of</p> <p>23 Valsartan API (TEA process)</p> <p>24 PRINSTON00075797 - 00076099</p>
Page 7	Page 9
<p>1 Also Present Remotely Via Zoom:</p> <p>2</p> <p>3 JUDY DIAZ, Videographer</p> <p>4 JESSICA DAVIDSON MILLER, ESQ., Skadden Arps</p> <p>5 CHRISTOPHER HENRY, Mazie Slater</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1 NUMBER DESCRIPTION PAGE</p> <p>2 Exhibit 6 Concise International Chemical 124</p> <p>3 Assessment Document 31, WHO,</p> <p>4 Geneva, 2001; N,N-DIMETHYLFORMAMIDE</p> <p>5 Exhibit 7 Shandong Hualu-Hengsheng 145</p> <p>6 Chemical Co., Ltd.,</p> <p>7 Certain of Analysis</p> <p>8 N,N-DIMETHYLFORMAMIDE</p> <p>9 Exhibit 8 International Union of Pure and 164</p> <p>10 Applied Chemistry, DIMETHYLFORMAMIDE:</p> <p>11 PURIFICATION, TESTS FOR PURITY AND</p> <p>12 PHYSICAL PROPERTIES, 1977</p> <p>13 Exhibit 9 Guidance For Industry, Genotoxic 222</p> <p>14 and Carcinogenic Impurities in Drug</p> <p>15 Substances and Products: Recommended</p> <p>16 Approaches, Draft Guidance,</p> <p>17 HHS-FDA-CDER, December 2008</p> <p>18 Exhibit 10 Investigation regarding unknown</p> <p>19 impurity (genotoxic impurity) of</p> <p>20 Valsartan API, 2018.07.08</p> <p>21 PRINSTON0076100 - 0076124</p> <p>22 Exhibit 11 Nitrosative Dealkylation of Some 256</p> <p>23 Symmetrical Tertiary Amines</p> <p>24 Gowenlock et al.</p>

<p style="text-align: right;">Page 10</p> <p>1 NUMBER DESCRIPTION PAGE</p> <p>2 Exhibit 12 Theoretical Investigation of 280</p> <p>3 N-Nitrosodimethylamine Formation</p> <p>4 from Nitrosation of Trimethylamine</p> <p>5 Sun et al., 2010</p> <p>6 ZHP01807298 - 7308</p> <p>7 Exhibit 13 Zhejiang Jianye Chemical Co., 320</p> <p>8 Ltd. Certificate of Analysis,</p> <p>9 November 25, 2012</p> <p>10 Triethylamine Analysis</p> <p>11 Exhibit 14 Zhejiang Huahai Pharmaceutical 325</p> <p>12 Co., Ltd., 2013-11-10</p> <p>13 Potential Impurities in Valsartan</p> <p>14 HUAHAI-US00007752 - 00007923</p> <p>15 Exhibit 15 Declaration of Seth A. Goldberg 343</p> <p>16 July 27, 2017</p> <p>17 Exhibit 16 Deposition of Min Li, Ph.D. 376</p> <p>18 April 22, 2021</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 12</p> <p>1 ---</p> <p>2 FENGtian XUE, PHD</p> <p>3 called for examination, and, after having been</p> <p>4 duly sworn, was examined and testified as</p> <p>5 follows:</p> <p>6 MR. BERNARDO: And I apologize</p> <p>7 for interrupting so quickly. I intended,</p> <p>8 Adam, to get this in before Jessica made</p> <p>9 a start.</p> <p>10 I just want to point out,</p> <p>11 Adam, that Dr. Xue has been recovering</p> <p>12 from COVID all week and has been powering</p> <p>13 through and is here and ready to go, as</p> <p>14 he'll tell you.</p> <p>15 I just want to ask for your</p> <p>16 patience because he may be soft-spoken at</p> <p>17 times, and I told him to try and speak up</p> <p>18 just because his voice is a little worn.</p> <p>19 And also we may have to ask for a break</p> <p>20 sooner than ordinarily, but I'm sure that</p> <p>21 won't present a problem.</p> <p>22 I just wanted to explain to</p> <p>23 you the reason for all that.</p> <p>24 MR. SLATER: Whatever it is,</p>
<p style="text-align: right;">Page 11</p> <p>1 PROCEEDINGS</p> <p>2 ---</p> <p>3 THE VIDEOGRAPHER: We are now</p> <p>4 on the record.</p> <p>5 My name is a Judy Diaz. I'm a</p> <p>6 legal videographer for Golkow Litigation</p> <p>7 Services. Today's date is February 3,</p> <p>8 2023 and the time is 10:04 a.m.</p> <p>9 This remote video deposition</p> <p>10 is being held in the matter of Valsartan,</p> <p>11 Losartan, and Irbesartan Products</p> <p>12 Liability Litigation MDL.</p> <p>13 The deponent is Fengtian Xue,</p> <p>14 PhD.</p> <p>15 All parties to this deposition</p> <p>16 are peering remotely and have agreed to</p> <p>17 the witness being sworn in remotely.</p> <p>18 All counsel will be noted on</p> <p>19 the stenographic record.</p> <p>20 The court reporter is Denise</p> <p>21 Vickery and will now swear in the</p> <p>22 witness.</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 13</p> <p>1 we're here for the duration. We are</p> <p>2 here.</p> <p>3 ---</p> <p>4 EXAMINATION</p> <p>5 ---</p> <p>6 BY MR. SLATER:</p> <p>7 Q. Hope you feel better. Hope you are</p> <p>8 feeling better, Doctor.</p> <p>9 A. Thank you.</p> <p>10 Q. Let me -- by the way, to pronounce</p> <p>11 your name tell me, the proper pronunciation</p> <p>12 please.</p> <p>13 A. Please call me Fengtian. Or you</p> <p>14 want me to --</p> <p>15 MR. BERNARDO: I think he's</p> <p>16 asking for how to pronounce your last</p> <p>17 name, Doctor.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Yes, Doctor, because I've heard it</p> <p>20 pronounced a few different ways. I want to make</p> <p>21 sure I get it right.</p> <p>22 A. What is the fast way "Xue."</p> <p>23 Q. Xue. Okay. I think I can handle</p> <p>24 that.</p>

<p style="text-align: right;">Page 14</p> <p>1 MR. SLATER: All right.</p> <p>2 Great. Are we on the record now?</p> <p>3 THE VIDEOGRAPHER: Yes, we're</p> <p>4 on the record.</p> <p>5 MR. SLATER: Okay. Great.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. Good morning, Dr. Xue.</p> <p>8 A. Good morning.</p> <p>9 Q. I'm Adam Slater. We've just</p> <p>10 introduced ourselves.</p> <p>11 You understand we're here to take</p> <p>12 your deposition, correct?</p> <p>13 A. I understand.</p> <p>14 Q. Have you ever had your deposition</p> <p>15 taken before?</p> <p>16 A. First time in my life.</p> <p>17 Q. There's a few important things that</p> <p>18 you should know.</p> <p>19 The one that's most important to me</p> <p>20 is that if you don't understand a question or it</p> <p>21 doesn't make sense to you for any reason such that</p> <p>22 you don't know if you can answer it truthfully or</p> <p>23 accurately, just say something. You can say, "I</p> <p>24 don't understand your question." Maybe you don't</p>	<p style="text-align: right;">Page 16</p> <p>1 form of the question." What he's saying is,</p> <p>2 Mr. Slater, you're not answering the -- asking the</p> <p>3 question properly under the rules of evidence.</p> <p>4 You may still answer the question.</p> <p>5 I would say in most cases you probably will. He's</p> <p>6 preserving his rights. I can re-ask the question</p> <p>7 differently. I can proceed with it. You</p> <p>8 shouldn't be thrown off by that.</p> <p>9 Just let -- if somebody objects,</p> <p>10 just let us address it, and then I would think for</p> <p>11 most -- and you'll get into the rhythm -- in most</p> <p>12 cases you'll probably just answer the question,</p> <p>13 but it's allowed. The lawyer is allowed to</p> <p>14 object. So just don't -- it's not -- not</p> <p>15 something you have to be concerned about, but</p> <p>16 you'll hear the objections from time to time.</p> <p>17 Okay?</p> <p>18 A. Okay.</p> <p>19 MR. SLATER: Let's first put</p> <p>20 up as Exhibit 1 the deposition notice.</p> <p>21 Actually, the responses and objections to</p> <p>22 the deposition notice. Let's do that.</p> <p>23 (Document marked for</p> <p>24 identification as Xue Exhibit 1.)</p>
<p style="text-align: right;">Page 15</p> <p>1 hear it. Maybe I mispronounce a scientific term.</p> <p>2 It could be for a whole host of reasons that you</p> <p>3 don't feel comfortable you understand what I'm</p> <p>4 asking.</p> <p>5 You can just tell me that. I might</p> <p>6 ask what's unclear. I might ask what the issue</p> <p>7 is. You can tell me, and I'll try to work to get</p> <p>8 a question out that you feel comfortable answering</p> <p>9 on the subject matter I'm trying to get into.</p> <p>10 Okay?</p> <p>11 A. Thank you.</p> <p>12 I also want to point out, I'm -- I</p> <p>13 speak English for 20-plus years but still my</p> <p>14 vocabulary is not the biggest. Sometimes if you</p> <p>15 speak a word, I may not be able to recognize what</p> <p>16 the meaning of the word. I may also point that</p> <p>17 out.</p> <p>18 Q. If for any reason you feel like you</p> <p>19 need clarification on anything I'm asking you, I</p> <p>20 want you to tell me.</p> <p>21 A. Thank you. I will do.</p> <p>22 Q. There may be objections during the</p> <p>23 course of the deposition. Lawyers are allowed to</p> <p>24 object. Mr. Bernardo can say, "Objection to the</p>	<p style="text-align: right;">Page 17</p> <p>1 MR. SLATER: Yeah, I'm --</p> <p>2 yeah, let's put it on the screen.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. Dr. Xue, did you review the</p> <p>5 deposition notice that we had served in advance of</p> <p>6 the deposition?</p> <p>7 A. Excuse me. Do I suppose to have</p> <p>8 this file also in the folder that sent to me?</p> <p>9 Q. I don't know the answer to that</p> <p>10 question.</p> <p>11 A. I just refreshed the folder that</p> <p>12 sent. Okay. Now I can see the file.</p> <p>13 Q. Okay. I'm actually not asking about</p> <p>14 this document yet. It's just on the screen. I'm</p> <p>15 asking a different question.</p> <p>16 A. Okay.</p> <p>17 Q. Did you see the deposition notice</p> <p>18 that was served in this case for your deposition?</p> <p>19 A. I am being seeing so many documents.</p> <p>20 Q. On -- on the screen, we have</p> <p>21 Exhibit 1, which is "Defendants' Responses and</p> <p>22 Objections to Plaintiffs' Notice to Take</p> <p>23 Videotaped Deposition." This is for -- this is</p> <p>24 the response by the attorneys to our request for</p>

<p style="text-align: right;">Page 18</p> <p>1 documents in advance of the deposition.</p> <p>2 Have you seen this response?</p> <p>3 A. I -- I think so. There's -- there's</p> <p>4 multiple items that I need to address there,</p> <p>5 right, to respond to those questions.</p> <p>6 Q. Did you do that? Did you go through</p> <p>7 the various requests and -- and make sure that</p> <p>8 anything that was requested was provided to the</p> <p>9 attorneys to provide to us?</p> <p>10 A. I think I did.</p> <p>11 MR. SLATER: Okay. Great.</p> <p>12 You can take that down.</p> <p>13 Let's put up as Exhibit 2, the</p> <p>14 report, please.</p> <p>15 (Document marked for</p> <p>16 identification as Xue Exhibit 2.)</p> <p>17 BY MR. SLATER:</p> <p>18 Q. We've put up on the screen</p> <p>19 Exhibit 2, which is the report we were served</p> <p>20 dated December 22, 2022, and it was signed by you</p> <p>21 at the end on page 58.</p> <p>22 Is that the report that you wrote in</p> <p>23 this case?</p> <p>24 A. Yes. You showed me the first page.</p>	<p style="text-align: right;">Page 20</p> <p>1 and Considered."</p> <p>2 Was that a complete list of the</p> <p>3 materials that you reviewed and considered as of</p> <p>4 the time that you authored your report dated</p> <p>5 December 22, 2022?</p> <p>6 A. Yes, I did all the -- my own search.</p> <p>7 Also the material provide by the counsels. I</p> <p>8 think everything that I considered when I write</p> <p>9 this report, offer my opinion, I put in that. I</p> <p>10 think it's called a list of material.</p> <p>11 MR. SLATER: Chris, can you go</p> <p>12 to that Exhibit A, please, the first</p> <p>13 page? Perfect.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. Looking at the Exhibit A to your</p> <p>16 report items 8, 9, and 10 are interviews with Min</p> <p>17 Li, Jucai Ge, and Jinsheng Lin.</p> <p>18 Do you see that?</p> <p>19 A. Yes, 8, 9, and 10 are the two --</p> <p>20 sorry -- three interviews.</p> <p>21 Q. Did you take notes of those</p> <p>22 interviews?</p> <p>23 A. I didn't take notes for neither of</p> <p>24 them.</p>
<p style="text-align: right;">Page 19</p> <p>1 By the first page, that is the report that I read.</p> <p>2 Q. And attached to the report --</p> <p>3 A. I'm sorry. I wrote, not read. I</p> <p>4 apologize.</p> <p>5 Q. Okay. Attached to the report was a</p> <p>6 curriculum vitae.</p> <p>7 Is that your up-to-date current</p> <p>8 curriculum vitae?</p> <p>9 A. Can you explain what "curriculum</p> <p>10 vitae" mean?</p> <p>11 Q. It's the list of your background,</p> <p>12 experience, your training, your education that we</p> <p>13 were provided.</p> <p>14 A. Oh. Oh.</p> <p>15 Q. It starts with your name at the top.</p> <p>16 It says that your title was associate professor,</p> <p>17 etc.</p> <p>18 A. Yeah. Sorry. I used to call it CV.</p> <p>19 You know, as I said, the word was not sound</p> <p>20 directly to me.</p> <p>21 Yes, I attach a copy of my CV to</p> <p>22 this report.</p> <p>23 Q. And then listed as Exhibit A to the</p> <p>24 report was something titled "Materials Reviewed</p>	<p style="text-align: right;">Page 21</p> <p>1 Q. Was anybody present when you</p> <p>2 interviewed those three people?</p> <p>3 A. Well, you mean besides me and the</p> <p>4 three people individual?</p> <p>5 Q. Correct.</p> <p>6 A. No, only a pair of us. Like if I</p> <p>7 interview Min Li, only Min Li and I was there.</p> <p>8 Q. Were -- were these interviews</p> <p>9 conducted in person or by some other means?</p> <p>10 A. All of them was through Internet.</p> <p>11 Q. Were you able to see each other?</p> <p>12 Was it by Zoom or something similar to Zoom?</p> <p>13 A. I didn't see them at all.</p> <p>14 Q. Were the interviews spoken or were</p> <p>15 they e-mails back and forth?</p> <p>16 A. I first reach out to them to make</p> <p>17 appointment. During the interview was just talk.</p> <p>18 Q. Do you know where each of those</p> <p>19 people were located when you interviewed them?</p> <p>20 A. Honestly, I don't know. I don't</p> <p>21 remember ask that question. I should not make</p> <p>22 speculation. I believe Jucai Ge and Dr. Jinsheng</p> <p>23 Lin was in China. Dr. Min Li might be in the U.S.</p> <p>24 Q. Had you ever met any of those people</p>

<p style="text-align: right;">Page 22</p> <p>1 before you interviewed them?</p> <p>2 A. I never met either of the three.</p> <p>3 Q. Were these interviews recorded?</p> <p>4 A. No, I didn't record any of the</p> <p>5 interviews.</p> <p>6 Q. When I went through your report, I</p> <p>7 did not see any reference to those interviews, any</p> <p>8 of the content of those interviews.</p> <p>9 Am I correct that nowhere in your</p> <p>10 report did you actually recite what those people</p> <p>11 told you during the interviews?</p> <p>12 A. Well, I talk them to them before I</p> <p>13 start writing my report. So some of the knowledge</p> <p>14 or information that I heard -- I heard from them I</p> <p>15 confirm with them my, you know, gave me idea that</p> <p>16 I -- that we think the conservation scope that I</p> <p>17 used to form my opinions.</p> <p>18 Q. In forming your opinions in this</p> <p>19 case, did you rely in part on those interviews</p> <p>20 with Min Li, Jucai Ge, and Jinsheng Lin?</p> <p>21 A. When you say "rely" means I cite</p> <p>22 them or I consider them. I just don't quite know</p> <p>23 what you really mean here.</p> <p>24 Q. In terms of the basis for the</p>	<p style="text-align: right;">Page 24</p> <p>1 something that they want me to know. As</p> <p>2 I said, I -- I consider that those when I</p> <p>3 form my opinions.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Did you speak with anybody else from</p> <p>6 ZHP or any of the companies affiliated with ZHP</p> <p>7 other than Min Li, Jucai Ge, and Jinsheng Lin with</p> <p>8 regard to this matter?</p> <p>9 A. With regard to this case, I never</p> <p>10 speak to anybody other than the three that listed</p> <p>11 here.</p> <p>12 Q. Before you were retained in this</p> <p>13 case, did you know anybody that has worked at ZHP</p> <p>14 or Princeton?</p> <p>15 A. No, I actually know nobody from</p> <p>16 those companies.</p> <p>17 Q. Do you know a toxicologist named</p> <p>18 Charles Wong?</p> <p>19 A. I have no idea because, you know,</p> <p>20 Charles Wong is a very common, you know, Chinese</p> <p>21 name.</p> <p>22 Q. I'm asking about a toxicologist</p> <p>23 named Charles Wong.</p> <p>24 A. No, I don't know any toxicologist</p>
<p style="text-align: right;">Page 23</p> <p>1 opinions you gave in your report --</p> <p>2 A. Right.</p> <p>3 Q. -- was one of the things that you</p> <p>4 relied on the interviews with Min Li, Jucai Ge,</p> <p>5 and Jinsheng Lin?</p> <p>6 MR. BERNARDO: Object to the</p> <p>7 form of the question. Vague.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. I'll ask the question again.</p> <p>10 In forming the opinions you formed</p> <p>11 in this case --</p> <p>12 A. Right.</p> <p>13 Q. -- was one of the things that you</p> <p>14 relied on the information you got from Min Li when</p> <p>15 you interviewed him?</p> <p>16 MR. BERNARDO: Object to the</p> <p>17 form of the question. Vague.</p> <p>18 THE WITNESS: As I said just</p> <p>19 now, when I interview not just Min Li,</p> <p>20 each one of the three ZHP employees, I</p> <p>21 had a conversation and they gave an</p> <p>22 introduction about what happened. I</p> <p>23 usually ask a couple questions.</p> <p>24 Yeah. They will highlight</p>	<p style="text-align: right;">Page 25</p> <p>1 named Charles Wong.</p> <p>2 Q. Is there any place in the report</p> <p>3 where you actually refer to anything that Min Li,</p> <p>4 Jucai Ge, or Jinsheng Lin told you during those</p> <p>5 interviews?</p> <p>6 I didn't see anything like that, but</p> <p>7 I'm asking if that's there and I missed it.</p> <p>8 A. I didn't cite anything that either</p> <p>9 one of the three people -- Jinsheng Lin, Jucai Ge,</p> <p>10 or Min Li -- told me.</p> <p>11 Q. There's a number of documents listed</p> <p>12 on this list of Materials Reviewed and Considered.</p> <p>13 Did you read every single one of the</p> <p>14 documents listed?</p> <p>15 A. I probably read every one. That's</p> <p>16 why it's listed here, but, you know, it has been a</p> <p>17 long journey. I've been reading so many</p> <p>18 documents, and also I did literature search on</p> <p>19 multiple reaction situations. I cannot say that I</p> <p>20 remember everything that I read and memorized</p> <p>21 because this report was written -- don't know --</p> <p>22 40 days ago. I honestly have been fairly busy</p> <p>23 and, on top of that, I've been suffer from COVID</p> <p>24 recently.</p>

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1 So I cannot say that I remember
2 everything that I -- I saw, but I'll try my best.
3 Q. Are you alone in that room that
4 you're in right now?
5 A. I am.
6 Q. Do you have any documents in hard
7 copy with you for this deposition?
8 A. Well, I have this plain report of
9 myself that you showing me in front of me. It's
10 closed. I'm not sure whether I'm allowed to read
11 it.
12 Q. Yes, you are.
13 A. Am I allowed to read my report?
14 Q. Yes.
15 A. Okay.
16 Q. I'm going to ask you at times about
17 the report, or if I ask questions and you need to
18 refer to the report, you can do so.
19 What I'm asking you right now is
20 just what documents you have. If you can just
21 list for me what you have out there.
22 A. That's the only -- only document I
23 have, other than the two screens in front of me.
24 Q. And when you say "the two screens,"

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1 one screen for the Zoom and then another screen
2 where you can electronically access documents?
3 A. Yes. So I have the screen. I see
4 you and I see everybody and see the document of
5 Exhibit A. On the other one, I have the folder.
6 It's called my name "Marked Exhibits" right now
7 showing on there.
8 MR. SLATER: You could take
9 that off the screen, Chris.
10 BY MR. SLATER:
11 Q. You said you have your report in
12 front of you. So I'm not going to need to put
13 the report up anymore. You can look at it.
14 Unless I need to show you a
15 particular thing, I can put it up, but it will
16 just be easier. You can look at it.
17 A. Yes, that's --
18 Q. You can look at something.
19 Your report sets forth various
20 opinions.
21 Are those all of the opinions that
22 you formed in this case at the time you wrote the
23 report?
24 A. So you talk about the three reports

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1 -- sorry -- three opinions on page 3?
2 Q. Those are your three opinions in
3 this case, the three bullet pointed opinions on
4 page 3?
5 A. Yes.
6 Q. You also wrote a supplemental
7 report.
8 MR. SLATER: Why don't we
9 throw that up, Chris, just to get it
10 identified.
11 Yeah, let's do as Exhibit 3
12 the supplemental report.
13 (Document marked for
14 identification as Xue Exhibit 3.)
15 BY MR. SLATER:
16 Q. Unless, Doctor, do you have that
17 handy also or do you only have your --
18 A. No. I didn't even know I'm allowed
19 to use the report. So I didn't print out the
20 supplementary. Maybe I have to --
21 Q. No problem.
22 A. -- put it up when I need it. Thank
23 you.
24 Q. Do you recognize Exhibit 3 as the

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1 supplemental report you wrote in this case dated
2 January 30, 2023?
3 A. Yes.
4 Q. It looked like this was a response
5 or a commentary on some of the testimony that was
6 given by Dr. Najafi in his deposition; is that
7 correct?
8 A. Yes, it is correct.
9 Q. Did you form any new opinions and
10 place those in that report, or did your opinions
11 as stated on page 3 of your first report remain
12 the same and did they remain as your only
13 opinions?
14 MR. BERNARDO: Object to the
15 form of the question. Vague.
16 BY MR. SLATER:
17 Q. I'll ask the question again.
18 Did you add any new opinions when
19 you wrote the supplemental report?
20 I didn't see any new opinions, but I
21 just want to make sure from your perspective you
22 didn't add any new opinions when you wrote the
23 supplemental report.
24 A. As he point out -- sorry.

<p style="text-align: right;">Page 30</p> <p>1 MR. BERNARDO: I was just</p> <p>2 going to object to the form of the</p> <p>3 question.</p> <p>4 But you can go on, Dr. Xue.</p> <p>5 THE WITNESS: As you point</p> <p>6 out, this report was written recently to</p> <p>7 address Dr. Najafi's deposition recent</p> <p>8 happened. I'm trying to use my knowledge</p> <p>9 in chemistry to address some of his</p> <p>10 statements.</p> <p>11 My main opinions are listed in</p> <p>12 my earlier report, the main report, the</p> <p>13 three points stays.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. The three opinions set forth in your</p> <p>16 initial report remain the same even when you wrote</p> <p>17 the supplemental report.</p> <p>18 Is that what you're telling me?</p> <p>19 I just want to confirm that.</p> <p>20 A. (Reviews document.)</p> <p>21 Q. Let me ask the question differently.</p> <p>22 A. I'm sorry. Yes, go ahead.</p> <p>23 MR. BERNARDO: I think he's</p> <p>24 just looking to confirm, Adam, just give</p>	<p style="text-align: right;">Page 32</p> <p>1 Q. We'll mark this as Exhibit 4.</p> <p>2 I saw that some depositions were</p> <p>3 added to the list of Dr. Hecht and Dr. Najafi and</p> <p>4 Dr. Plunkett.</p> <p>5 To your knowledge, was anything else</p> <p>6 added to this amended and supplemental list as</p> <p>7 compared to the original list?</p> <p>8 A. I add because these, you said those</p> <p>9 three depositions happened after my original</p> <p>10 report, and I reviewed them. So I want to add</p> <p>11 these depositions to the material conservation.</p> <p>12 Also, I also add a paper that was --</p> <p>13 it's just one paper I want to add to that as well.</p> <p>14 Q. Which paper was that?</p> <p>15 A. I honestly don't remember exactly</p> <p>16 what the paper's title was, but it -- yeah, I can</p> <p>17 look through to -- to find it. Is that --</p> <p>18 Q. Do you recall why you wanted to add</p> <p>19 that paper? What the subject matter was?</p> <p>20 A. Well, because that's just when I --</p> <p>21 when I originally write the report. There's a</p> <p>22 bunch of examples of reaction conditions I want to</p> <p>23 support. So I did literature search. I found</p> <p>24 these maybe -- I don't know -- few dozens of</p>
<p style="text-align: right;">Page 31</p> <p>1 him a moment.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. Yeah.</p> <p>4 A. Yeah, I just want to make sure</p> <p>5 everything I said is -- is --</p> <p>6 Q. Oh, I didn't realize you were</p> <p>7 looking at the report to answer the question.</p> <p>8 Go ahead. I'm sorry. Go ahead.</p> <p>9 A. Yeah.</p> <p>10 Q. And just for the record, the</p> <p>11 question is: The supplemental report did not</p> <p>12 change or add any new opinions; is that correct?</p> <p>13 A. I'll agree there's no additional</p> <p>14 point that I want to add. I just want to address</p> <p>15 the -- the comments or points that Dr. Najafi</p> <p>16 raised during his deposition recently.</p> <p>17 MR. SLATER: And just to be</p> <p>18 fair, with regard to the reliance list,</p> <p>19 let's mark as Exhibit 4 the "Amended and</p> <p>20 Supplemental List of Materials Reviewed</p> <p>21 and Considered."</p> <p>22 (Document marked for</p> <p>23 identification as Xue Exhibit 4.)</p> <p>24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 33</p> <p>1 papers and those are one of that.</p> <p>2 And I honestly don't remember what</p> <p>3 was the reason, but I just put on -- I run</p> <p>4 literature and I recognize later on, and then I</p> <p>5 decide to just give the counsel that additional</p> <p>6 paper.</p> <p>7 Q. We also received an e-mail</p> <p>8 yesterday, February 2nd, that indicated that when</p> <p>9 you were preparing for this deposition, you</p> <p>10 noticed that a few of the deposition transcripts</p> <p>11 you reviewed were inadvertently omitted from the</p> <p>12 list of materials considered, including Jucai Ge</p> <p>13 deposition May 26 and May 27, 2022 and Pang Dong</p> <p>14 deposition April 1, 2021.</p> <p>15 Is that correct that you also had</p> <p>16 read those depositions?</p> <p>17 A. Oh, I did.</p> <p>18 Q. Did you read the deposition</p> <p>19 transcripts complete from cover to cover?</p> <p>20 A. I honestly won't say that. Because</p> <p>21 especially Jucai Ge's it's very long. I won't say</p> <p>22 I read line to line every line, but I cover most</p> <p>23 of part when I prepared for my -- for my report.</p> <p>24 For -- for Dong -- I forgot his</p>

<p style="text-align: right;">Page 34</p> <p>1 first name -- that deposition I only read a small 2 portion. Because that I remember was I asked for 3 this deposition because Dr. Najafi or maybe 4 Dr. Hecht -- I forgot -- during their deposition, 5 they use this as their additional, one of the 6 papers, 2010, some -- some therapeutic studies -- 7 sorry -- theoretical calculations where that paper 8 came to me as part of Pang Dong's deposition, and 9 that's why I ask for the counsel to sent me his 10 deposition to look. 11 But I didn't look Pang Dong's for 12 the most part. 13 MR. SLATER: We can take down 14 that reliance list. 15 BY MR. SLATER: 16 Q. I want to ask you a couple questions 17 about your report again, the initial report, 18 December 22, 2022, Exhibit 2. 19 A. Yes. 20 Q. The report lists a lot of facts, 21 some in great detail, a lot of information. 22 Would that be information that you 23 felt was most important to you in forming your 24 opinions in this case? Is that why that</p>	<p style="text-align: right;">Page 36</p> <p>1 then I see their points and then I try to 2 address their points in a way that my 3 understanding of the science behind the 4 case. Like the nitrosamines, NDMA's, 5 NDEAs, these process. That's what I -- 6 what I did. 7 I cannot really see that I 8 highlight everything. Mostly we need to 9 focus on what the experts on the 10 plaintiff side talked about. 11 BY MR. SLATER: 12 Q. You prepared for this deposition, 13 right? 14 Did you prepare for this deposition? 15 Did you prepare yourself? 16 A. I did. You see what (indicates). 17 Q. Okay. Is one of the things you did 18 in preparing for the deposition reading your 19 report? 20 MR. BERNARDO: Object to the 21 form of the question. Vague. 22 THE WITNESS: Well, I don't -- 23 BY MR. SLATER: 24 Q. Dr. Xue, it's a very simple</p>
<p style="text-align: right;">Page 35</p> <p>1 information is what you actually discussed in the 2 report? 3 A. When I write report or any art -- 4 scientific papers I wrote in my career, I always 5 trying to present my opinion or my discovery in a 6 way that I highlighting the case. I use some 7 avenues to support my -- my -- my point. If I 8 have opinion overall in scientific writing we call 9 it conclusions, I usually also highlight that in 10 the writing. So that's just my style. 11 I -- I guess I hope that answer your 12 question. 13 Q. My question is: The facts that you 14 discussed in your report. 15 A. Right. 16 Q. Are those the facts that were most 17 important to you in forming your opinions? 18 MR. BERNARDO: Object to the 19 form of the question. Vague. 20 THE WITNESS: Well, I can only 21 say that these are the fact that I, you 22 know, I read. When I write this report, 23 I mostly read the plaintiffs' experts' 24 report from, I think, four experts, and</p>	<p style="text-align: right;">Page 37</p> <p>1 question. 2 A. I know. 3 Q. Did you read your report as part of 4 your preparation for today's deposition? 5 MR. BERNARDO: Object to the 6 form of the question. Argumentative. 7 Go on, Dr. Xue. 8 THE WITNESS: I wrote my 9 report. I read my report. 10 BY MR. SLATER: 11 Q. So the answer is yes? 12 MR. BERNARDO: Object to the 13 form of the question. Vague. 14 Adam, why don't you ask him 15 the question. From what he demonstrated 16 with his attire, I think it's clear he 17 didn't understand what you meant by 18 prepared. 19 He's trying to be very 20 responsive as I can tell, but I think he 21 pointed out at the very beginning of this 22 deposition some language issues. So if 23 you could just re-ask the question, I 24 think he didn't understand it.</p>

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1 MR. SLATER: Okay.

2 BY MR. SLATER:

3 Q. Dr. Xue.

4 A. Yes.

5 Q. Did you review documents, including

6 your report, in order to prepare yourself to

7 answer questions today during the deposition?

8 A. Oh, yeah, I did read my report.

9 Q. That's all I asked.

10 A. Okay. Thank you. I -- yeah.

11 Q. When you read the report in

12 preparation for the deposition, did you think to

13 yourself that there were any important facts that

14 you're relying on that were not discussed in the

15 report?

16 A. I read my report. I honestly never

17 ask myself that question. I review all my core

18 key opinions stay because I -- this is not

19 something come to me simply, right? So I know

20 this is important case. I did my study. I formed

21 them, these -- these -- these opinions.

22 Yeah. I definitely read my report

23 before the deposition, but I -- I don't think I,

24 you know, I will question myself. This is

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1 something I seriously prepared.

2 Q. Are there any facts that are

3 important to you that you're relying on to support

4 the opinions you gave that are not in your report,

5 that are not discussed in the report? Anything

6 you can point to?

7 The answer may be nothing. I just

8 want to know if there's anything outside the

9 report factually that you're relying on that's not

10 discussed in the report that you can tell me right

11 now.

12 It's a yes-or-no question.

13 A. Can I get a confirmation? Are you

14 asking whether every single point that I rely on

15 to form this report is covered or listed in my

16 report? Is that your question?

17 Q. My question is: Are there any facts

18 that are important to you in forming your

19 opinions?

20 A. Right.

21 Q. Facts that you're relying on to say,

22 "This is my opinion. It's based on this." Where

23 you would say, "I didn't talk about that fact in

24 my report."

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1 Is there anything like that?

2 MR. BERNARDO: Object to the

3 form of the question. Vague. Broad.

4 THE WITNESS: I honestly -- I

5 cannot answer this question with a yes or

6 no. Because, you know, writing papers or

7 writing reports is, it's everything come

8 to me. I read. I digest the opinions

9 from the experts on -- on the plaintiff

10 side. Excuse me.

11 And then I do my own little

12 search. I digest the case. Understand

13 each piece, what the science told me, and

14 then I form my own.

15 Like as you just read, there

16 are three key things. I don't know

17 whether I can say every single fact was

18 addressed or shown in the -- in my

19 report. Yeah.

20 I hope that answer your

21 question.

22 BY MR. SLATER:

23 Q. When I read your report, both your

24 reports, I did not see any criticisms by you of

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1 ZHP.

2 Are there any opinions that you have

3 in any of your reports where you criticize

4 anything ZHP did?

5 A. Well, I -- I just -- I think I

6 explain this just now, right? So I --

7 Q. It's a yes-or-no question, Doctor.

8 Let me ask it again because I think you're -- I

9 don't know what you're -- you may not have been

10 deposed before, but if you're going to give me

11 long stories in response to questions that are

12 simple yes or noes, we're going to go much longer

13 than necessary.

14 So let me try it again with you.

15 MR. BERNARDO: Objection.

16 BY MR. SLATER:

17 Q. Make it a smaller question for you.

18 Are there any criticisms of ZHP in

19 either of your reports?

20 A. I really tried my best to help. I'm

21 not trying to not answer short, right? But these

22 questions are not to me yes or no questions.

23 Q. All right. Well, then, let me ask

24 it again so that I try to get it to a yes or no.

<p style="text-align: right;">Page 42</p> <p>1 Do you have any opinions critical of</p> <p>2 ZHP where you're saying ZHP did something wrong or</p> <p>3 failed to do something it should have done?</p> <p>4 A. I'm -- I was retained by the ZHP</p> <p>5 counsel to offer my opinion to address the</p> <p>6 plaintiffs' experts' point and since during I read</p> <p>7 all these report from the plaintiffs' experts.</p> <p>8 They were saying everything ZHP did was wrong,</p> <p>9 right? So I was trying to address that.</p> <p>10 So I really don't feel that I -- I</p> <p>11 have any, you know, when I approach this, come up</p> <p>12 with the report, I don't have any intention to do</p> <p>13 so.</p> <p>14 Q. No intention to criticize ZHP in any</p> <p>15 way? Is that what you mean when you said --</p> <p>16 listen, let me ask it again.</p> <p>17 When you said, "I had no intention</p> <p>18 to do so," did you -- were you saying you had no</p> <p>19 intention to criticize ZHP? Is that what you</p> <p>20 meant when you said "to do so," yes or no?</p> <p>21 A. Well, I probably didn't make myself</p> <p>22 clear. If that's my language issue, I already</p> <p>23 said I feel sorry about that. But I tried to</p> <p>24 explain, right?</p>	<p style="text-align: right;">Page 44</p> <p>1 You just told me you were responding</p> <p>2 to the plaintiffs' experts.</p> <p>3 Was there anything else that you</p> <p>4 thought was your role in this case?</p> <p>5 A. My role is, I was retained by the</p> <p>6 ZHP counsel as an expert in organic chemistry to</p> <p>7 offer my own opinion about this whole case, and I</p> <p>8 was also given or, you know, provided the</p> <p>9 material, including the major material was the</p> <p>10 four report from the plaintiffs' experts. Of</p> <p>11 course, they have a lot of citation in there as</p> <p>12 well.</p> <p>13 Yeah. So that's the scope of my --</p> <p>14 my role here I thought because I'm an organic</p> <p>15 chemist. I might offer some expertise in my area.</p> <p>16 I try to understand the whole case throughout</p> <p>17 reading all the -- all the informations available</p> <p>18 to me, and I did my own search as well to see what</p> <p>19 the science was about at that time when they</p> <p>20 actually developed these processes, all these</p> <p>21 things. And then I come up with a report.</p> <p>22 That's my understanding about --</p> <p>23 sorry -- my role here.</p> <p>24 Q. Did you form any opinions during</p>
<p style="text-align: right;">Page 43</p> <p>1 So I'm here as a -- as an expert in</p> <p>2 organic chemistry trying to address the experts on</p> <p>3 the plaintiff side points and then that's how, you</p> <p>4 know, I form my report around that theme.</p> <p>5 So I'm -- in other words, I'm really</p> <p>6 -- I don't -- I'm not here to criticize anybody.</p> <p>7 I just want to address the point that the</p> <p>8 plaintiffs' expert offered.</p> <p>9 I hope that answer your question.</p> <p>10 Q. It does and it's helpful because it</p> <p>11 was something I was going to get into in a few</p> <p>12 minutes. So you brought me there so we can go</p> <p>13 there now.</p> <p>14 I think what you're -- what you're</p> <p>15 telling me is that you -- rephrase.</p> <p>16 I think what you're telling me is</p> <p>17 you understood your role in this case to respond</p> <p>18 to the plaintiff expert reports in the field of</p> <p>19 organic chemistry; is that correct?</p> <p>20 A. I disagree.</p> <p>21 Q. Okay. Let me ask a different</p> <p>22 question then.</p> <p>23 What is your understanding of what</p> <p>24 your role was as an expert in this case?</p>	<p style="text-align: right;">Page 45</p> <p>1 your work as an expert in this case where the</p> <p>2 opinion is that ZHP either did something that it</p> <p>3 should not have done or failed to do something</p> <p>4 that it should have done?</p> <p>5 A. Well --</p> <p>6 Q. Actually, let me ask the question</p> <p>7 differently.</p> <p>8 As you sit here now --</p> <p>9 A. Right.</p> <p>10 Q. -- as an expert, do you have any</p> <p>11 criticisms of ZHP?</p> <p>12 MR. BERNARDO: Object to the</p> <p>13 form of the question. Asked and</p> <p>14 answered.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. You can answer, Doctor.</p> <p>17 Do you have any opinions critical of</p> <p>18 ZHP?</p> <p>19 MR. BERNARDO: Object to the</p> <p>20 form of the question. Vague.</p> <p>21 THE WITNESS: I really don't</p> <p>22 want to repeat myself but --</p> <p>23 BY MR. SLATER:</p> <p>24 Q. It's a yes-or-no question, Doctor.</p>

<p style="text-align: right;">Page 46</p> <p>1 A. As I said, I really tried if I can 2 answer yes or no, that would be easy. I really 3 cannot because this is, like I mention that I was 4 retained as organic chemist to offer my opinion 5 about the case. I offered all these effort report 6 from the experts from the plaintiff side. I read 7 them. I digest them. I do my own search. 8 Yeah. So I -- these three, as you 9 just read the three, are my -- my -- my opinions. 10 That's -- that I think is clear. 11 Q. Yeah. I'm asking you now. 12 A. Okay. 13 Q. As you sit here now. 14 A. Right. 15 Q. Do you have the opinion that ZHP did 16 anything wrong? 17 A. Okay. So -- 18 MR. BERNARDO: Wait. Wait. 19 Object to the form of the 20 question. And, Adam, he's trying to 21 respond. I think the scope of his 22 opinions are clearly delineated. He's 23 trying to explain that in his report. 24 He's here to offer an opinion</p>	<p style="text-align: right;">Page 48</p> <p>1 BY MR. SLATER: 2 Q. Doctor -- 3 MR. BERNARDO: I'm simply 4 preserving my objection. 5 MR. SLATER: That's okay. I'm 6 going to ask a question. 7 BY MR. SLATER: 8 Q. Doctor, as an expert in this case, 9 did you consider whether or not ZHP failed to do 10 anything in connection with the development of the 11 manufacturing processes at issue in this case? 12 Did you think -- 13 MR. BERNARDO: Object. 14 BY MR. SLATER: 15 Q. -- about that whether or not ZHP 16 failed to do anything it should have done? 17 MR. BERNARDO: Object to the 18 form of the question. Vague. Overly 19 broad. Asked and answered. 20 You can answer, Dr. Xue. 21 BY MR. SLATER: 22 Q. All right. You can answer. 23 A. I'll try one last time. I really -- 24 Q. It's a yes-or-no question, Doctor.</p>
<p style="text-align: right;">Page 47</p> <p>1 about organic chemistry, not company 2 conduct. He's tried to answer your 3 question. This sort of goes back to the 4 hearing I recall with Judge Vanaskie 5 saying, you know, you can ask it several 6 times and then move on. So I object -- 7 MR. SLATER: Rich. Rich. 8 MR. BERNARDO: I object -- 9 MR. SLATER: Don't talk with 10 me right now, please. That's -- you're 11 totally out of line. 12 MR. BERNARDO: I object to 13 this continued line of questions. Go on. 14 MR. SLATER: That's okay. I 15 have a witness who's having a hard time 16 even understanding or responding to my 17 questions, and you're giving me a hard 18 time about following up? 19 MR. BERNARDO: I think the 20 witness -- 21 MR. SLATER: I'm taking the 22 deposition now, okay? If you want to put 23 it in that context, then we'll -- then 24 we'll get much more direct.</p>	<p style="text-align: right;">Page 49</p> <p>1 MR. BERNARDO: Adam, please 2 don't interrupt him -- 3 THE WITNESS: As I said -- 4 MR. BERNARDO: -- with saying 5 it's a yes-or-no question. It is not a 6 yes-or-no question, and he's trying to 7 say that. Judge Vanaskie has already -- 8 MR. SLATER: That's great. 9 You're obstructing this deposition very 10 early on. I don't appreciate it. 11 MR. BERNARDO: I disagree. 12 MR. SLATER: And please don't 13 threaten me with court action. 14 MR. BERNARDO: I didn't 15 threaten you with court action. 16 MR. SLATER: You did. You 17 did. 18 MR. BERNARDO: I'm just 19 observing -- 20 MR. SLATER: You're wasting 21 time on my record right now. 22 MR. BERNARDO: Adam, I think 23 you're wasting time now. 24 BY MR. SLATER:</p>

<p style="text-align: right;">Page 50</p> <p>1 Q. Answer the question.</p> <p>2 Doctor, a new question.</p> <p>3 As part of your review of this case,</p> <p>4 did you consider whether ZHP failed to do anything</p> <p>5 from an organic chemistry perspective that it</p> <p>6 should have done?</p> <p>7 MR. BERNARDO: Object to the</p> <p>8 form of the question. Vague. Overly</p> <p>9 broad. Asked and answered.</p> <p>10 Go ahead, Dr. Xue.</p> <p>11 THE WITNESS: As I said, I</p> <p>12 really cannot say yes or no for this</p> <p>13 question.</p> <p>14 I'm an organic chemist. I --</p> <p>15 I review what ZHP did. They did the</p> <p>16 planning. They did the risk assessment.</p> <p>17 They did the testings. And I also, of</p> <p>18 course, read all the report from the</p> <p>19 plaintiff side about these issues.</p> <p>20 And then I went out myself.</p> <p>21 As I pointed again and again, I'm a</p> <p>22 chemist. I went out to just search for</p> <p>23 the chemistry, what I rely on, what I</p> <p>24 steps myself, and what I'm here for.</p>	<p style="text-align: right;">Page 52</p> <p>1 A. I have this report. I think the</p> <p>2 opinions are there, right? So there that the</p> <p>3 three bullets that we read upfront was my opinion.</p> <p>4 Q. So the answer is, no, you have no</p> <p>5 opinions in your report critical of ZHP; is that</p> <p>6 correct?</p> <p>7 MR. BERNARDO: Object to the</p> <p>8 form of the question.</p> <p>9 THE WITNESS: Well -- well, I</p> <p>10 think we are -- we are making circles</p> <p>11 here, right? So we talk about this for I</p> <p>12 don't know how long, but this -- I</p> <p>13 describe my view of my role here. I</p> <p>14 stick with that.</p> <p>15 I tried to be an expert to do</p> <p>16 my job and tried to offer my opinion</p> <p>17 based on my search, my understanding of</p> <p>18 the case.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. Doctor, do you know what you wrote</p> <p>21 in your report?</p> <p>22 A. I do. I wrote the report myself.</p> <p>23 Q. Right.</p> <p>24 Are there any opinions in your</p>
<p style="text-align: right;">Page 51</p> <p>1 So I read all these things.</p> <p>2 That form the three points. I mean, for</p> <p>3 -- for -- for ZHP, they did what they can</p> <p>4 at the time the knowledge available to</p> <p>5 them.</p> <p>6 I hope -- I really hope that</p> <p>7 answer your question.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. I read your report. I saw no --</p> <p>10 A. Excuse me.</p> <p>11 Q. Okay. I'll start over.</p> <p>12 I saw your report. I saw no</p> <p>13 opinions critical of ZHP in your reports.</p> <p>14 Were there any opinions in your</p> <p>15 reports critical of ZHP?</p> <p>16 MR. BERNARDO: Object to the</p> <p>17 form of the question. Asked and</p> <p>18 answered.</p> <p>19 You can go ahead, Dr. Xue.</p> <p>20 THE WITNESS: Are you asking</p> <p>21 in my -- my report I'm facing now is</p> <p>22 there any opinion criticizing ZHP?</p> <p>23 BY MR. SLATER:</p> <p>24 Q. That's my question.</p>	<p style="text-align: right;">Page 53</p> <p>1 report critical of ZHP?</p> <p>2 It's a yes-or-no question. I didn't</p> <p>3 see any. I just want to confirm I didn't miss it.</p> <p>4 MR. BERNARDO: Object to the</p> <p>5 form of the question.</p> <p>6 THE WITNESS: Well, I'll try</p> <p>7 one more time.</p> <p>8 I offered my opinion based on</p> <p>9 what I search, what I learned, what I</p> <p>10 read, and what I believe.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. I did not see any opinions in your</p> <p>13 report criticizing ZHP.</p> <p>14 Am I correct that there are no</p> <p>15 opinions you wrote in the report where you</p> <p>16 criticized ZHP?</p> <p>17 MR. BERNARDO: Object to the</p> <p>18 form of the question. Asked and</p> <p>19 answered.</p> <p>20 Go ahead, Dr. Xue.</p> <p>21 THE WITNESS: I have the</p> <p>22 three opinions, right, out there. ZHP,</p> <p>23 they did what they can, right? They</p> <p>24 don't have -- based on what they have</p>

<p style="text-align: right;">Page 54</p> <p>1 specifically at the time when all these</p> <p>2 processes they developing. That's what</p> <p>3 available to them. So that's what --</p> <p>4 what I form opinion.</p> <p>5 I'm not -- sometimes those --</p> <p>6 a lot of things it's not like absolute,</p> <p>7 right? So, yes, it must be like this.</p> <p>8 It must be like that, right?</p> <p>9 So I have to judge based on my</p> <p>10 own expertise, based on what other people</p> <p>11 talk, and what I learn from the science</p> <p>12 to come up with a reasonable, appropriate</p> <p>13 judgment of myself.</p> <p>14 I really think that that --</p> <p>15 that that's what I do here.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Did you read the deviation</p> <p>18 investigation reports written by ZHP?</p> <p>19 A. Well, I -- I read you know, right?</p> <p>20 So this is big case. I read so many documents.</p> <p>21 Q. Doctor, do you know what the</p> <p>22 deviation investigation reports are? Do you know</p> <p>23 what those documents are?</p> <p>24 A. I think those are -- if you -- do</p>	<p style="text-align: right;">Page 56</p> <p>1 MR. SLATER: You can put it on</p> <p>2 the screen.</p> <p>3 THE WITNESS: I just got it</p> <p>4 loaded on my screen.</p> <p>5 As I said, I read so many</p> <p>6 things. This looks --</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Doctor, I'm not asking you about all</p> <p>9 the things you read.</p> <p>10 I'm literally asking you: Have you</p> <p>11 read this document?</p> <p>12 A. I saw this document before, but as I</p> <p>13 said, if you want me -- ask me about details in</p> <p>14 here, I need to kind of -- you need to direct me</p> <p>15 there so I cite. I don't know. This --</p> <p>16 Q. Doctor.</p> <p>17 A. This is 300 pages.</p> <p>18 Q. Dr. Xue, we're going to do much</p> <p>19 better today if you answer the questions I'm</p> <p>20 answering and then don't go and tell me something</p> <p>21 else. Like I wasn't asking you about whether I'm</p> <p>22 going to ask you questions.</p> <p>23 I asked you one question. The</p> <p>24 question is: Did you see this deviation</p>
<p style="text-align: right;">Page 55</p> <p>1 you have the document? Can we see the document</p> <p>2 together?</p> <p>3 Q. Sure.</p> <p>4 MR. SLATER: Let's put up the</p> <p>5 one that we've been talking about that we</p> <p>6 were talking about before. I guess it</p> <p>7 was Exhibit 210. The E318003 version 2.</p> <p>8 Put that on the screen.</p> <p>9 THE WITNESS: Will that be</p> <p>10 Exhibit Number 5?</p> <p>11 MR. SLATER: That will be</p> <p>12 Exhibit Number 5.</p> <p>13 (Document marked for</p> <p>14 identification as Xue Exhibit 5.)</p> <p>15 BY MR. SLATER:</p> <p>16 Q. For the record, he's uploading --</p> <p>17 we're uploading as Exhibit --</p> <p>18 For the record, we've uploaded</p> <p>19 Exhibit 5, which is the November 5, 2018 deviation</p> <p>20 investigation report titled "Investigation</p> <p>21 regarding unknown impurity" and then in</p> <p>22 parentheses "(genotoxic impurity) of Valsartan API</p> <p>23 (TEA process)."</p> <p>24 Do you have that? Do you see it?</p>	<p style="text-align: right;">Page 57</p> <p>1 investigation report?</p> <p>2 A. I do.</p> <p>3 Q. Yes or no?</p> <p>4 A. I do.</p> <p>5 MR. BERNARDO: Object to the</p> <p>6 form of the question.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Did you consider this report in</p> <p>9 forming your opinions in this case?</p> <p>10 A. So all the document that's made</p> <p>11 available, I read them and then I judge, and then</p> <p>12 I decide to form my report. So in that case, yes,</p> <p>13 I did consider everything including this</p> <p>14 particular one to form my opinion.</p> <p>15 Q. As you sit here now, have you formed</p> <p>16 any opinions -- well, rephrase.</p> <p>17 As you sit here now, do you have any</p> <p>18 disagreement with any of the conclusions that ZHP</p> <p>19 formed and documented in this deviation</p> <p>20 investigation report?</p> <p>21 MR. BERNARDO: Object to the</p> <p>22 form of the question. Vague. Overly</p> <p>23 broad. Goes beyond the scope of his</p> <p>24 disclosure as an expert.</p>

<p style="text-align: right;">Page 58</p> <p>1 Go ahead, Dr. Xue.</p> <p>2 MR. SLATER: Let's keep our</p> <p>3 objections to good-faith objections, too.</p> <p>4 MR. BERNARDO: You have to</p> <p>5 explain to me what remotely was in bad</p> <p>6 faith about an objection that, pursuant</p> <p>7 to Judge Vanaskie's instruction, gives</p> <p>8 you as simply as possible some</p> <p>9 understanding. That was as cryptic as I</p> <p>10 can be, Adam.</p> <p>11 MR. SLATER: Okay.</p> <p>12 THE WITNESS: Well --</p> <p>13 BY MR. SLATER:</p> <p>14 Q. Answer the question, Doctor.</p> <p>15 A. I will try to answer. Can you --</p> <p>16 the question is kind of long. Can you chop it</p> <p>17 into small pieces so I can handle?</p> <p>18 Q. Okay. Do you know what a deviation</p> <p>19 investigation report is? Do you know what this</p> <p>20 document is?</p> <p>21 A. Yes. This document was actually in</p> <p>22 2018 in July. That's after the nitrosamine was</p> <p>23 already known to be in some of the batches of the</p> <p>24 valsartan API, and then they did -- I think this</p>	<p style="text-align: right;">Page 60</p> <p>1 questions. So that's what I need.</p> <p>2 So I'm going to ask you this.</p> <p>3 I read your report. I did not see</p> <p>4 anywhere in your report where you said that any</p> <p>5 conclusion or finding by ZHP in its deviation</p> <p>6 investigation reports that you disagree with any</p> <p>7 of those conclusions or findings.</p> <p>8 Do you disagree with any of ZHP's</p> <p>9 conclusions or findings that were placed in their</p> <p>10 deviation investigation report?</p> <p>11 MR. BERNARDO: Object to the</p> <p>12 form of the question. Beyond the scope</p> <p>13 of his disclosure. Overly broad.</p> <p>14 Go ahead, Dr. Xue.</p> <p>15 THE WITNESS: Well, if you can</p> <p>16 show me.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. No, I'm not. Doctor, let's stop</p> <p>19 right there. I'm not going to show you.</p> <p>20 MR. BERNARDO: No, no, no.</p> <p>21 Let's stop interrupting the witness,</p> <p>22 who's simply asking if you could show him</p> <p>23 something to refresh his recollection,</p> <p>24 he'll answer. Okay? So let's stop the</p>
<p style="text-align: right;">Page 59</p> <p>1 is like a retrospective or backward study. That's</p> <p>2 my understanding about this.</p> <p>3 Q. Did you see that during the course</p> <p>4 of this report ZHP drew certain conclusions and</p> <p>5 made certain findings? Did you -- did you notice</p> <p>6 that when you read the report?</p> <p>7 MR. BERNARDO: Object to the</p> <p>8 form of the question. Overly broad.</p> <p>9 THE WITNESS: Right. As I</p> <p>10 said, this is like -- although you don't</p> <p>11 like my comments, but this is 300 pages.</p> <p>12 I honestly I don't have a super good</p> <p>13 memory about everything I read.</p> <p>14 If you can, please, if you can</p> <p>15 point to the section that you want me to</p> <p>16 address. Because I honestly I can't</p> <p>17 really just off my head to say everything</p> <p>18 or memorize everything you talk about</p> <p>19 here.</p> <p>20 I -- I really try my best</p> <p>21 tried to help everybody here.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. It's not -- with all due respect, I</p> <p>24 don't need help. What I need is answers to my</p>	<p style="text-align: right;">Page 61</p> <p>1 interrupting each other.</p> <p>2 THE WITNESS: I'm --</p> <p>3 BY MR. SLATER:</p> <p>4 Q. That's not the question, though. So</p> <p>5 that's --</p> <p>6 A. I'm here --</p> <p>7 Q. I withdraw the question, Doctor,</p> <p>8 because we're -- we're honestly at some point I'm</p> <p>9 going to stop the deposition if I cannot get</p> <p>10 intelligible answers to questions, and I'm just</p> <p>11 going to send the transcript to the court and say</p> <p>12 that counsel needs to reprep their witness to be</p> <p>13 able to actually answer a question with a direct</p> <p>14 answer.</p> <p>15 It's not the ground we covered.</p> <p>16 MR. BERNARDO: Now I object.</p> <p>17 That's a threat. That's --</p> <p>18 MR. SLATER: No. I'm feeling</p> <p>19 very frustrated because I cannot get an</p> <p>20 answer to a question.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. And so here's the question, Doctor.</p> <p>23 A. Yes.</p> <p>24 Q. If you disagreed with any of Z --</p>

<p style="text-align: right;">Page 62</p> <p>1 well, let me ask the question differently.</p> <p>2 As a general matter, you understand</p> <p>3 that in the deviation investigation report, ZHP</p> <p>4 analyzed why the NDMA and NDEA contamination</p> <p>5 occurred in its valsartan API.</p> <p>6 Do you understand generally that was</p> <p>7 the purpose of this document?</p> <p>8 A. That -- that's something. At least</p> <p>9 to my understand, that's something included in</p> <p>10 this study.</p> <p>11 Q. Okay. Do you disagree with any of</p> <p>12 the findings or conclusions by ZHP that they</p> <p>13 documented in analyzing what happened?</p> <p>14 MR. BERNARDO: Objection.</p> <p>15 THE WITNESS: Well, here's --</p> <p>16 MR. BERNARDO: Wait a minute,</p> <p>17 Doctor.</p> <p>18 Object to the form of the</p> <p>19 question. Vague. Overly broad. Beyond</p> <p>20 the scope of his disclosure.</p> <p>21 Go ahead, Dr. Xue.</p> <p>22 THE WITNESS: Well, as I said,</p> <p>23 right? So if you ask me whether I</p> <p>24 disagree with some conclusion, I think I</p>	<p style="text-align: right;">Page 64</p> <p>1 I'm here as a chemist addressing the</p> <p>2 experts' opinions from the plaintiff side. If</p> <p>3 they raise anything, I try to address. I read the</p> <p>4 whole thing. I, you know, I tried to look for my</p> <p>5 scientific basis to address those.</p> <p>6 I don't know why you think -- or</p> <p>7 maybe I'm wrong -- I should actually be</p> <p>8 responsible also for finding any evidence to prove</p> <p>9 that ZHP did anything wrong.</p> <p>10 Q. Doctor, I'm not trying to evaluate</p> <p>11 anything other than to confirm that I didn't see a</p> <p>12 particular opinion in your report.</p> <p>13 So all I'm asking you is this.</p> <p>14 You wrote a report dated</p> <p>15 December 22, 2022.</p> <p>16 A. Right.</p> <p>17 Q. I don't see any opinion in that</p> <p>18 report, which is 58 pages long, where you said</p> <p>19 that ZHP made a finding or drew a conclusion in a</p> <p>20 deviation investigation report that you disagree</p> <p>21 with.</p> <p>22 I just want to make sure that you</p> <p>23 can confirm for me, "Yes, you're right,</p> <p>24 Mr. Slater, I didn't form such an opinion and put</p>
<p style="text-align: right;">Page 63</p> <p>1 have at least the right to know what</p> <p>2 conclusion you talk about here, right?</p> <p>3 So also these regulatory work</p> <p>4 is really -- we are moving kind of</p> <p>5 outside of my -- my expertise.</p> <p>6 I try to do everything that I</p> <p>7 can to offer in my -- in my area, but if</p> <p>8 you don't even show me what -- what</p> <p>9 conclusion you are talking about here</p> <p>10 and -- and what at least really chemistry</p> <p>11 related or -- or it's not even my area.</p> <p>12 I just don't want to get</p> <p>13 anywhere that is -- is not my expertise.</p> <p>14 I'm sorry.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Okay. I read your report very</p> <p>17 carefully, Doctor. I did not see any opinions in</p> <p>18 your report where you said that ZHP made a finding</p> <p>19 in a deviation investigation report that you</p> <p>20 disagree with.</p> <p>21 There's no such opinion in your</p> <p>22 report, right?</p> <p>23 A. Well, because what we -- I think we</p> <p>24 kind of moving back to the last question.</p>	<p style="text-align: right;">Page 65</p> <p>1 it in my report." That's all I'm asking.</p> <p>2 Am I right?</p> <p>3 MR. BERNARDO: Dr. Xue, he's</p> <p>4 simply asking to confirm that what he</p> <p>5 said is not written in your report.</p> <p>6 Just --</p> <p>7 THE WITNESS: Right.</p> <p>8 I think I answered that</p> <p>9 because I have the three, three bullets,</p> <p>10 three opinions I wrote clearly. Beyond</p> <p>11 that, that's not my key opinions. I --</p> <p>12 yeah. So that means I don't have those</p> <p>13 opinions. The three key opinions I</p> <p>14 listed clearly in my report already.</p> <p>15 That make sense to you?</p> <p>16 BY MR. SLATER:</p> <p>17 Q. You're holding yourself out as an</p> <p>18 expert in this case as an expert in the field of</p> <p>19 organic chemistry; is that correct?</p> <p>20 A. Yes.</p> <p>21 Q. Do you hold yourself out as an</p> <p>22 expert with regard to the FDA?</p> <p>23 A. Can you clarify what "FDA" mean</p> <p>24 here?</p>

<p style="text-align: right;">Page 66</p> <p>1 Q. Are you holding yourself out as an</p> <p>2 expert with regard to the FDA's oversight of the</p> <p>3 API manufacturing process for drugs like</p> <p>4 valsartan?</p> <p>5 A. Can you also explain to me what</p> <p>6 "oversight" mean?</p> <p>7 Q. You don't know what "FDA oversight"</p> <p>8 means?</p> <p>9 A. I see oversight as like -- like</p> <p>10 supervise, oversee. So but specifically, what do</p> <p>11 you mean by "oversight"? Are you talking about</p> <p>12 FDA regulations?</p> <p>13 Q. I will ask it differently.</p> <p>14 Are you holding yourself out as an</p> <p>15 expert with regard to FDA regulation of the</p> <p>16 development and manufacture of drug products?</p> <p>17 A. On the regulation part, as I made it</p> <p>18 clear, I'm not expert at all in regulatory</p> <p>19 science.</p> <p>20 But in term of drug development</p> <p>21 or -- or those technical processes involving</p> <p>22 organic chemistry, because the nature of my own</p> <p>23 research and training, I have those background.</p> <p>24 Q. The part you just told me about at</p>	<p style="text-align: right;">Page 68</p> <p>1 your question, not trying to cut you adding</p> <p>2 additional useless information there. I'm really</p> <p>3 trying to help.</p> <p>4 Q. You're not holding yourself out as</p> <p>5 an expert with regard to Good Manufacturing</p> <p>6 Practices, correct?</p> <p>7 A. I know GMP, but I'm -- I'm here, as</p> <p>8 I said upfront, I'm an organic chemist. I'm here</p> <p>9 for that, but I know GMP, but I'm not an expert in</p> <p>10 those regulations so those -- those -- those rules</p> <p>11 of things.</p> <p>12 Q. From reading your CV, it's my</p> <p>13 understanding that you do -- well, actually, why</p> <p>14 don't you tell me in a simple short version what</p> <p>15 it is that you do professionally.</p> <p>16 A. I'm an associate professor. I do</p> <p>17 therapeutic development. I own a lab. We -- we</p> <p>18 -- we -- what we work on multiple projects try to</p> <p>19 develop different drugs for different type of</p> <p>20 human diseases.</p> <p>21 Q. And I saw a term small molecule --</p> <p>22 "small molecule therapeutics"?</p> <p>23 A. Yes.</p> <p>24 Q. What does that mean?</p>
<p style="text-align: right;">Page 67</p> <p>1 the end of your answer is not what I asked you</p> <p>2 about.</p> <p>3 I asked about the FDA regulation of</p> <p>4 drug development and drug manufacturing.</p> <p>5 You're not an expert in that area,</p> <p>6 correct?</p> <p>7 A. Well, if that's, again, my language</p> <p>8 apologize, but I think your question was not quite</p> <p>9 what you are saying, right?</p> <p>10 So you are saying I judge myself as</p> <p>11 the expert in manufacturing, development. All</p> <p>12 these are not just regulatory. These are -- these</p> <p>13 are matching my field, right? These are reaction</p> <p>14 involved, the chemistry involved and then you</p> <p>15 have, you know, there are all these judgment, all</p> <p>16 these assessment or testing, those are there,</p> <p>17 right?</p> <p>18 So, but if you talk about regulation</p> <p>19 like what is required? What -- what -- what is</p> <p>20 GMP? What -- what are those, you know, for</p> <p>21 different things, APIs, what the standard of this?</p> <p>22 That's where I am not.</p> <p>23 I want to make it clear. This is</p> <p>24 not -- I thought just now I was trying to answer</p>	<p style="text-align: right;">Page 69</p> <p>1 A. Thank you for reading my CV.</p> <p>2 Q. What are small -- rephrase.</p> <p>3 I saw in your CV the term "small</p> <p>4 molecule --</p> <p>5 A. Yeah.</p> <p>6 Q. -- therapeutics." What does that</p> <p>7 mean?</p> <p>8 A. Small molecule like, for instance,</p> <p>9 we all know valsartan is a small molecule. So</p> <p>10 therapeutics means drugs. Like valsartan, you</p> <p>11 know, is a -- is a small molecule drug. So that's</p> <p>12 what I do.</p> <p>13 Q. You develop the -- the molecules</p> <p>14 that actually are going to have an impact</p> <p>15 physiologically on a person's body to address a</p> <p>16 disease basically?</p> <p>17 A. That's our goal. We haven't really</p> <p>18 got anything on the market yet.</p> <p>19 Q. Are you involved in the development</p> <p>20 of a drug product for manufacture and sale on a</p> <p>21 commercial basis? Meaning after you develop or</p> <p>22 work on developing the molecule, are you then</p> <p>23 involved in if a pharmaceutical company -- well,</p> <p>24 let me ask the question differently.</p>

<p style="text-align: right;">Page 70</p> <p>1 Do you have any experience working</p> <p>2 with the actual development of a manufacturing</p> <p>3 process for large-scale manufacturing of a drug</p> <p>4 product for commercial sale? Is that something</p> <p>5 that you've done?</p> <p>6 A. Well, for marketing, put things</p> <p>7 advertisement or setting or, you know, all these,</p> <p>8 I have no clue. I have never done those.</p> <p>9 But for development, right? So for</p> <p>10 just point out the FDA purpose, I never really</p> <p>11 involved in the regulations or registers, all</p> <p>12 these thing. Although we try and move there.</p> <p>13 So, but what we do here is a lot of</p> <p>14 research. It's close to identification,</p> <p>15 synthesis, development, characterization of the</p> <p>16 compound and, of course, we do animal variation,</p> <p>17 big or small animals. So the goal is to put</p> <p>18 things on market.</p> <p>19 So I don't know whether that answer</p> <p>20 your question.</p> <p>21 So a lot of my thing, my -- my -- my</p> <p>22 research scope is -- is stopped before like</p> <p>23 packaging, dosing or -- or advertisement.</p> <p>24 I don't know whether that answer</p>	<p style="text-align: right;">Page 72</p> <p>1 their project cross.</p> <p>2 Just like zinc chloride like you use</p> <p>3 as example. We don't do zinc chloride. We don't</p> <p>4 do valsartan at all in our lab. But we --</p> <p>5 everybody has -- has some sort of project.</p> <p>6 They all trying to make the compound</p> <p>7 in the efficiency that they want, and then they</p> <p>8 try to get the compound characterized in the high</p> <p>9 quality as much as we want. And then they want to</p> <p>10 make sure they can finish the project in a time</p> <p>11 efficient way means they don't want to get caught</p> <p>12 in trouble because they didn't plan well.</p> <p>13 So all these are I think it's -- I</p> <p>14 personally have never worked for any</p> <p>15 pharmaceutical company in my career, but our lab,</p> <p>16 the nature of the research -- I won't -- I won't</p> <p>17 say. Maybe it's not the good analogy, but it's</p> <p>18 like a mini pharmaceutical industry here ongoing</p> <p>19 in my lab.</p> <p>20 Q. Have you ever developed an API for</p> <p>21 commercial manufacture?</p> <p>22 A. You're asking whether I have</p> <p>23 developed, right? So as I said, that's my goal,</p> <p>24 right? So to, you know, to get a drug on market</p>
<p style="text-align: right;">Page 71</p> <p>1 your question.</p> <p>2 Q. Well, let me give you -- try to do</p> <p>3 it with using some of the terms from this case.</p> <p>4 One of the manufacturing processes</p> <p>5 at issue in this case we've referred to as the</p> <p>6 zinc chloride process, correct?</p> <p>7 A. Oh, yes.</p> <p>8 Q. Okay. In your work, have you been</p> <p>9 involved in developing a drug -- drug</p> <p>10 manufacturing process such as like the zinc</p> <p>11 chloride process?</p> <p>12 Meaning the drug manufacturing at a</p> <p>13 pharmaceutical company where they're actually</p> <p>14 going to manufacture the pills from the API, etc.,</p> <p>15 that's not something you do, right?</p> <p>16 A. Well, what you just described is a</p> <p>17 little broad. Like as I said, right? So we don't</p> <p>18 do manufacture in term of get to the dose like you</p> <p>19 got really commercial boxes to the patient. We</p> <p>20 don't do that.</p> <p>21 However, my research or my work is a</p> <p>22 lot of development, just like the -- the reaction.</p> <p>23 I mean, we have to evaluate reaction. We have to</p> <p>24 read. Everyday everybody in my lab has to have</p>	<p style="text-align: right;">Page 73</p> <p>1 to help people with their health. I haven't had</p> <p>2 any drug named after me at this moment.</p> <p>3 Q. Have you ever been involved in the</p> <p>4 development of a manufacturing process for an API</p> <p>5 for a pharmaceutical company to actually</p> <p>6 manufacture the API? Has that something -- is</p> <p>7 that something you've ever done?</p> <p>8 A. So you asking whether I'm involved</p> <p>9 in partnership with a -- with a pharmaceutical</p> <p>10 company?</p> <p>11 Q. In any capacity.</p> <p>12 Have you ever done that?</p> <p>13 A. So we have collaborative projects</p> <p>14 sometimes with companies. I don't know whether</p> <p>15 that -- that qualified or that's what you were</p> <p>16 asking. But we -- as I said, we -- our research</p> <p>17 nature is very close to pharmaceutical company</p> <p>18 does. We don't worry about the product, you know,</p> <p>19 formulations or dosing or advertisement or</p> <p>20 selling. We don't. We never get in touch of</p> <p>21 that, but everything else actually we do.</p> <p>22 Q. Let's talk about valsartan and try</p> <p>23 to talk in that context.</p> <p>24 A. Sure.</p>

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<p>1 Q. What you do is you try to develop --</p> <p>2 if we use -- if we used valsartan -- let me ask it</p> <p>3 differently.</p> <p>4 What you do is you try -- you're the</p> <p>5 person who develops the valsartan molecule to</p> <p>6 treat high blood pressure.</p> <p>7 That's -- that's what you do</p> <p>8 basically, right?</p> <p>9 I know you didn't develop valsartan,</p> <p>10 but by analogy, that's what your research is to</p> <p>11 develop the actual -- the actual drug that's going</p> <p>12 to actually -- the molecule, the valsartan</p> <p>13 molecule.</p> <p>14 That's basically what you'd be</p> <p>15 developing, right?</p> <p>16 A. That's not quite the same.</p> <p>17 See, what we do is we have a</p> <p>18 variation this compound. Let's see valsartan. As</p> <p>19 you said, we don't do valsartan in the lab. I</p> <p>20 just want to make it clear.</p> <p>21 Valsartan is my target now. We need</p> <p>22 to figure out how to make valsartan in the lab in</p> <p>23 an efficient way because PhD thesis probably</p> <p>24 depends on the time. So they need to be very</p>	<p>1 coming from something, right? So you're going to</p> <p>2 have some design strategy there to come with a</p> <p>3 structure. However, this is like a first sector,</p> <p>4 first stage.</p> <p>5 Then the next stage is also super</p> <p>6 important is to make sure you produce in a timely</p> <p>7 fashion and a quality fashion a nice molecule. So</p> <p>8 you can use that for all the testing, PKs, PDs</p> <p>9 animal studies, toxicologies. All these things we</p> <p>10 do, that depends on the -- on the second sector</p> <p>11 the synthesis.</p> <p>12 So we have three sectors. Just now</p> <p>13 you're saying I try to identify the structure.</p> <p>14 That's absolutely a very, very important sector,</p> <p>15 but it's not complete.</p> <p>16 Q. Have you ever had input into the</p> <p>17 development of a manufacturing process for an API?</p> <p>18 MR. BERNARDO: Object to the</p> <p>19 form of the question. Vague.</p> <p>20 THE WITNESS: Right. So I</p> <p>21 spent a little time just now. I thought</p> <p>22 I made it fairly clear, right?</p> <p>23 So what I don't do is, I don't</p> <p>24 do those regulatories. When I -- when</p>
Page 75	Page 77
<p>1 carefully work with me, design a synthetic route,</p> <p>2 and that would be used by the PhD student to get</p> <p>3 the valsartan synthesized.</p> <p>4 And then we want to make sure we</p> <p>5 have good quality control of the valsartan product</p> <p>6 that we got is in good shape. So that means you</p> <p>7 can actually use that through all these testing.</p> <p>8 And then we will -- we will -- we</p> <p>9 will validate valsartan does control the blood</p> <p>10 pressure in different models, in vitro, in vivo.</p> <p>11 And then we will -- we will say, hey, FDA, we have</p> <p>12 something. Please give us, you know, drug</p> <p>13 approval. But that -- we never touch that yet.</p> <p>14 That's the goal.</p> <p>15 Q. Your focus is on developing the</p> <p>16 structure of the drug to treat the medical</p> <p>17 condition. That's what your research and that's</p> <p>18 what your work is focused on.</p> <p>19 Do I understand that?</p> <p>20 A. Well, I think you -- your -- your</p> <p>21 point is close, but not quite complete. Because</p> <p>22 my work, yes, is very, very critical for my -- my</p> <p>23 people to actually get the structure.</p> <p>24 Like valsartan, you can imagine it's</p>	<p>1 you have a compound that's ready, we know</p> <p>2 all everything was great. We just need</p> <p>3 to make the pill and packaging.</p> <p>4 We don't do that. We have no</p> <p>5 expertise. We don't -- I honestly have</p> <p>6 no interest in touching that in my</p> <p>7 personal career. But what everything</p> <p>8 else a drug development process requires,</p> <p>9 my lab does them all.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. Do you know what an API is?</p> <p>12 A. Yes.</p> <p>13 Q. What is an API?</p> <p>14 A. It's active pharmaceutical -- excuse</p> <p>15 me -- it's the ingredient. Sorry about that.</p> <p>16 Q. In your career up to today --</p> <p>17 A. Yeah.</p> <p>18 Q. -- have you ever been involved in</p> <p>19 the development of the manufacturing process for</p> <p>20 an API that was actually sold?</p> <p>21 A. Well, to answer your question</p> <p>22 like -- like yes or no question, right? So if</p> <p>23 this is like -- you ask me whether I have a drug</p> <p>24 on market. I thought I already told you. I hope</p>

<p style="text-align: right;">Page 78</p> <p>1 I do. This moment I don't have any drug already 2 be approved. We have multiple project on the way. 3 I also have grant -- I'm not having 4 yet. Hopefully, it will be founded. But have 5 pending grant at FDA. They try -- I try to, you 6 know, they are trying to fund me on something like 7 you said to develop directly an API on the market, 8 but not -- the grant is still pending. I cannot 9 -- I hope I can get it. 10 Q. So up till today, you've never been 11 involved in the development of an API that was 12 actually sold on the market, correct? 13 A. No, it's not correct, right? So -- 14 Q. So tell me -- then tell me -- 15 MR. BERNARDO: Wait, wait. 16 BY MR. SLATER: 17 Q. -- which supply you have developed 18 that's actually on the market? 19 MR. BERNARDO: Object to the 20 form of the question, and he said that's 21 not correct and clearly was -- 22 MR. SLATER: Actually, you 23 know what? I misstated my question 24 actually, and I meant to ask about the</p>	<p style="text-align: right;">Page 80</p> <p>1 MR. BERNARDO: Object. 2 THE WITNESS: Yeah. 3 MR. BERNARDO: Let's stop 4 interrupting the witness's question. 5 MR. SLATER: How about we 6 suggest to our witness to answer the 7 question directly? I think we both have 8 objections here. 9 THE WITNESS: I -- I really 10 trying, right? So I said if you ask me 11 whether I have a drug on market after my 12 name -- 13 BY MR. SLATER: 14 Q. I'm not asking that. 15 A. I don't -- 16 Q. Don't answer that, Doctor. 17 I didn't ask you about your name or 18 whether you own the drug. That's not the question 19 I asked. 20 So let's try to focus on the 21 question now. 22 A. Yeah. 23 Q. Let's be precise. 24 A. Right.</p>
<p style="text-align: right;">Page 79</p> <p>1 manufacturing process. 2 BY MR. SLATER: 3 Q. Let me ask you this differently. 4 So am I correct that up until today, 5 you have not yet ever developed or been involved 6 in the development of the manufacturing process 7 for an API that was actually sold on the market? 8 Have you ever done that up till 9 today? 10 MR. BERNARDO: Object to the 11 form of the question. Asked and 12 answered. 13 BY MR. SLATER: 14 Q. It's a yes or no, sir. 15 MR. BERNARDO: Object to the 16 form of the question. 17 THE WITNESS: You keep 18 saying. You keep saying the question yes 19 or noes. I also try to answer if it can 20 be a yes or no, but it is not, right? 21 BY MR. SLATER: 22 Q. Have you -- 23 A. I said -- 24 Q. Have you --</p>	<p style="text-align: right;">Page 81</p> <p>1 Q. Up until today, have you ever been 2 involved in the development of the manufacturing 3 process for any API that was actually sold on the 4 market? 5 MR. BERNARDO: Object to the 6 form of the question. 7 BY MR. SLATER: 8 Q. Yes or no. Have you done that or 9 have you not done it? 10 A. Yeah. So I think I get the 11 question. 12 If you ask me whether any of the 13 market drug at this moment was developed by me, 14 the answer is, no, I haven't developed any drug 15 that is sold on market at this moment. 16 I hope my next drug will be sold on 17 market next year or very soon. We are doing 18 those, but I hope it's in the near future. 19 If you say right now, Dr. Xue, if 20 you have any drug already sold or you involve in 21 any compound that is already be sold on market, 22 it's not, but it doesn't mean I'm not doing those, 23 right? 24 MR. BERNARDO: Adam, we've</p>

<p style="text-align: right;">Page 82</p> <p>1 been going about an hour and 15. If this 2 is a good breaking point?</p> <p>3 MR. SLATER: I'm ready to keep 4 going. So you guys like to do your hour 5 break. You do whatever you want. If you 6 want to stop the deposition and take a 7 break, you have the right to do it. I 8 don't need a break.</p> <p>9 MR. BERNARDO: Dr. Xue, would 10 you like a break?</p> <p>11 THE WITNESS: Yes.</p> <p>12 MR. BERNARDO: Okay. We'll 13 take a break.</p> <p>14 MR. SLATER: See you in 10 15 minutes.</p> <p>16 THE VIDEOGRAPHER: Time right 17 now is 11:17 a.m. We're off the record. 18 (Recess.)</p> <p>19 THE VIDEOGRAPHER: Time right 20 now is 11:29 a.m. We're back on the 21 record.</p> <p>22 BY MR. SLATER: 23 Q. Dr. Xue, do you utilize gas 24 chromatography in your lab?</p>	<p style="text-align: right;">Page 84</p> <p>1 does someone else do that?</p> <p>2 A. I sometimes do that myself.</p> <p>3 Sometimes my student do them. Sometimes if it's 4 high-end experiment, the collaborators in the mass 5 spec center will do that themselves just to 6 protect the improvement.</p> <p>7 Q. Have you ever used any form of 8 chromatography or mass spectrometry to try to 9 identify a nitrosamine in a substance?</p> <p>10 A. I never used -- you said 11 chromatography -- either GC or LC to identify 12 nitrosamine in my career.</p> <p>13 Q. Have you ever used mass spectrometry 14 to try to isolate or identify a nitrosamine?</p> <p>15 A. I never in my career do that.</p> <p>16 Q. Do you hold yourself out as an 17 expert with regard to the formation and 18 identification of nitrosamines?</p> <p>19 A. You're asking I view myself as an 20 expert for the formation and you said isolation as 21 well for nitrosamine?</p> <p>22 Q. Do you hold yourself out as an 23 expert with regard to the identification and 24 formation of nitrosamines?</p>
<p style="text-align: right;">Page 83</p> <p>1 A. In my lab, we don't use gas 2 chromatography.</p> <p>3 Q. Have you ever used gas 4 chromatography for any of your work?</p> <p>5 A. In graduate school, we used GC for 6 some works when I was a graduate student. But, 7 you know, in general speaking, because the nature 8 of my research, we work on molecules that are not, 9 like very small, like a solvent size.</p> <p>10 So we do mass spec. We -- we do 11 chromatography but usually liquid chromatography. 12 They are same concept but different nature because 13 the requirement of the size of the molecule.</p> <p>14 Q. You utilize -- rephrase. 15 Do you use liquid chromatography in 16 your -- in your work?</p> <p>17 A. Yes.</p> <p>18 Q. Do you use -- 19 A. Instead of GC. 20 Q. Do you use liquid 21 chromatography-mass spectrometry in your work?</p> <p>22 A. I do use L -- we call it LC-MS -- 23 liquid chromatography-MS in my work a lot.</p> <p>24 Q. Do you operate the LC-MS machine or</p>	<p style="text-align: right;">Page 85</p> <p>1 A. Thank you for repeating.</p> <p>2 For nitrosamines specifically as a 3 class of compound, I never did in my research.</p> <p>4 But in term of small molecule characterization and 5 formation, we do that on daily basis. That's the 6 nature the majority of our research do.</p> <p>7 Q. When did you first learn of the NDMA 8 and NDEA contamination of valsartan?</p> <p>9 A. When I start to get involved in this 10 case, I learned these two small molecules NDMA and 11 NDEA contamination for valsartan API.</p> <p>12 Q. According to the invoices that we 13 were provided, your first meeting took place 14 November 18, 2022 with Jessica and Allison.</p> <p>15 Is that the first time you were 16 contacted regarding this case?</p> <p>17 A. I don't remember exactly the date I 18 put. It's a while ago, but that was not the first 19 time I was contacted.</p> <p>20 Q. The date of the first meeting on 21 your invoice is November 18, 2022.</p> <p>22 When were you first contacted?</p> <p>23 A. I believe it's probably three, maybe 24 four days before that first meeting. I really</p>

<p style="text-align: right;">Page 86</p> <p>1 honestly don't remember exact how many days.</p> <p>2 Q. I don't know I need -- I don't need</p> <p>3 to know the exact date.</p> <p>4 A. Okay. A few -- a few days before</p> <p>5 the meeting, Jessica Miller, Ms. Jessica Miller</p> <p>6 called me.</p> <p>7 Q. So you first learned about the NDMA</p> <p>8 and NDEA contamination of valsartan in November</p> <p>9 2022, correct?</p> <p>10 A. Yes.</p> <p>11 Q. In terms of the root cause for the</p> <p>12 formation of the NDMA -- you understand what root</p> <p>13 cause means?</p> <p>14 A. If I understand correctly, root</p> <p>15 cause is like why. Is that the correct meaning of</p> <p>16 root cause?</p> <p>17 Q. We can go with that for now.</p> <p>18 A. Okay. Thank you.</p> <p>19 Q. If we boil down the root cause to</p> <p>20 the very simple, the most -- the most fundamental</p> <p>21 reason why this, the NDMA formed in the zinc</p> <p>22 chloride process --</p> <p>23 A. Your voice was chopped off because</p> <p>24 it was -- I think the Internet. Can you repeat</p>	<p style="text-align: right;">Page 88</p> <p>1 THE WITNESS: The quenching</p> <p>2 process of the -- you said the zinc</p> <p>3 chloride process, right?</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Let me start over.</p> <p>6 A. Okay.</p> <p>7 Q. You know what? Actually, I'm not</p> <p>8 going to waste my time with this.</p> <p>9 Let's now talk about a couple other</p> <p>10 things.</p> <p>11 In your report, at one point you</p> <p>12 talk about reaction environments.</p> <p>13 When you use the term a "reaction</p> <p>14 environment," would an example of a reaction</p> <p>15 environment be the zinc chloride process?</p> <p>16 A. You want me to provide an example or</p> <p>17 you want --</p> <p>18 Q. No. I just want to know if</p> <p>19 that's -- if my understanding is correct or not.</p> <p>20 A. What was your understanding? So</p> <p>21 you --</p> <p>22 Q. Is an example of a reaction</p> <p>23 environment the zinc chloride process?</p> <p>24 A. A zinc chloride process is multiple</p>
<p style="text-align: right;">Page 87</p> <p>1 what you just say?</p> <p>2 Q. Sure.</p> <p>3 Was the quenching of valsartan with</p> <p>4 sodium nitrite part of the root cause for the</p> <p>5 creation of the NDMA in the zinc chloride process?</p> <p>6 A. I apologize, but just now your voice</p> <p>7 was still -- you freeze for like three seconds.</p> <p>8 MR. SLATER: Am I freezing?</p> <p>9 BY MR. SLATER:</p> <p>10 Q. Might be on your end.</p> <p>11 MR. BERNARDO: I think,</p> <p>12 Dr. Xue, it might be on your end because</p> <p>13 he was pretty clear on my end.</p> <p>14 THE WITNESS: I heard you</p> <p>15 talk about sodium nitrate, but before</p> <p>16 that there were three second I didn't</p> <p>17 quite hear what you say.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Was the quenching with sodium</p> <p>20 nitrite as part of the zinc chloride process an</p> <p>21 important part of why the NDMA formed?</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. Vague.</p> <p>24 Go on.</p>	<p style="text-align: right;">Page 89</p> <p>1 step. It's -- I think we can call it four or five</p> <p>2 steps, right? Reaction in the environment is a</p> <p>3 specific set of conditions that's specific for the</p> <p>4 particular reaction.</p> <p>5 It's -- it's -- I think for zinc</p> <p>6 chloride process, it's too big of a scope for</p> <p>7 environment because you want to -- you want to be</p> <p>8 more specific on what specific reaction you talk</p> <p>9 about.</p> <p>10 Q. Would the tetrazole ring formation</p> <p>11 step of the zinc chloride process be an example of</p> <p>12 a reaction environment?</p> <p>13 A. Yes, you can say that.</p> <p>14 Q. Would the quenching step be a</p> <p>15 reaction environment?</p> <p>16 A. Quenching step is also, yes. It's a</p> <p>17 -- we usually call it reaction conditions, but</p> <p>18 yeah. So environment is similar to conditions.</p> <p>19 Q. One of the points that you make in</p> <p>20 your -- rephrase.</p> <p>21 One of the subjects that you address</p> <p>22 in your report is the temperature at which the</p> <p>23 zinc chloride tetrazole ring formation step took</p> <p>24 place at.</p>

<p style="text-align: right;">Page 90</p> <p>1 You discuss temperature in your 2 report, right?</p> <p>3 A. I did.</p> <p>4 Q. And if I understand your opinion, 5 it's your opinion that the temperature that the 6 DMF was subjected to was too low for DMA to form. 7 Is that your opinion?</p> <p>8 A. My opinion is ZHP at that moment, 9 not now, but when they actually develop and use 10 the zinc chloride process, they have no idea that 11 DMF can actually decompose at the temperature that 12 they run. I believe is 135 -- 335 degrees C.</p> <p>13 Q. Are you aware that ZHP never even 14 considered the question of whether or not the DMF 15 could degrade during the process?</p> <p>16 Are you aware they did not even 17 consider the question or analyze it at all?</p> <p>18 A. So you're asking --</p> <p>19 MR. BERNARDO: Object to the 20 question.</p> <p>21 THE WITNESS: -- me to confirm 22 that ZHP never aware that the 23 decomposition of DMF could actually take 24 place in their tetrazole reaction? Is</p>	<p style="text-align: right;">Page 92</p> <p>1 MR. BERNARDO: Then you 2 shouldn't engage me, Adam.</p> <p>3 MR. SLATER: I'm not going to. 4 That's the last time it will happen 5 today.</p> <p>6 MR. BERNARDO: Perfect.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Can you answer the question, Doctor?</p> <p>9 A. I'm sorry. Can you repeat? I just 10 got lost.</p> <p>11 Q. Sure. Sure. 12 Are you aware that ZHP did not 13 consider the question of whether or not DMF could 14 degrade during the zinc chloride process to give 15 off dimethylamine?</p> <p>16 Are you aware they never even 17 thought about the question of whether or not it 18 could happen?</p> <p>19 MR. BERNARDO: Object to the 20 form of the question.</p> <p>21 THE WITNESS: Well, based on 22 what I read, right, there's really not 23 much available. They were not -- they 24 didn't know and there's not actually</p>
<p style="text-align: right;">Page 91</p> <p>1 that your question?</p> <p>2 BY MR. SLATER:</p> <p>3 Q. My question was different. 4 My question is: Are you aware that 5 ZHP didn't even consider the question, didn't even 6 think about the question of whether or not the DMF 7 could degrade under the conditions of the zinc 8 chloride process?</p> <p>9 Are you aware they never even 10 thought about that?</p> <p>11 MR. BERNARDO: Object to the 12 form of the question. Vague. Beyond the 13 scope of his --</p> <p>14 MR. SLATER: You're objecting? 15 There's a stipulation that you entered 16 into with me on this point.</p> <p>17 MR. BERNARDO: Well, then, you 18 don't need to ask this witness about it.</p> <p>19 MR. SLATER: All right. Let's 20 not go back and forth. You and I, we 21 should not communicate during this 22 deposition. It's not going well.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Doctor --</p>	<p style="text-align: right;">Page 93</p> <p>1 reasonable to expect them to know.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. Can you answer my question now?</p> <p>4 A. So the question was, did I aware 5 they didn't even consider, right?</p> <p>6 I cannot speculate for other people 7 whether they consider or not, but my research 8 under my told me that, first of all, they didn't 9 know. Second, they have not reasonably be 10 expected to know this.</p> <p>11 That's my -- I -- I cannot say -- I 12 cannot speak for ZHP, right?</p> <p>13 Q. Well, you're an expert in this case. 14 Do you understand that you're 15 supposed to be objective?</p> <p>16 MR. BERNARDO: Object to the 17 form of the question. We're getting --</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Let me ask the question differently 20 because counsel didn't like my question. 21 Did you try to be objective in this 22 case?</p> <p>23 It's a simple yes or no. Did you 24 try to be objective?</p>

<p style="text-align: right;">Page 94</p> <p>1 A. Yes.</p> <p>2 Q. So if you want to be an objective</p> <p>3 expert, you want to see, well, did ZHP do anything</p> <p>4 wrong?</p> <p>5 That's one of the things you should</p> <p>6 have been thinking about to be an objective</p> <p>7 expert, right?</p> <p>8 MR. BERNARDO: Object to the</p> <p>9 form of the question. Argumentative.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. Correct?</p> <p>12 A. I consider everything come to me to</p> <p>13 decide what I believe is correct or what I believe</p> <p>14 is wrong.</p> <p>15 Q. Okay. In forming your opinions, you</p> <p>16 had to rely on the facts that were provided to</p> <p>17 you, right? You had to rely on the facts,</p> <p>18 correct?</p> <p>19 A. For that I definitely agree, I rely</p> <p>20 on the fact. I rely on everything that actually</p> <p>21 provided I found around this topic.</p> <p>22 Q. Okay. And in terms of the facts</p> <p>23 that you relied on, did you understand whether or</p> <p>24 not ZHP even considered the possibility that DMF</p>	<p style="text-align: right;">Page 96</p> <p>1 right?</p> <p>2 MR. BERNARDO: Object to the</p> <p>3 form of the question. Vague.</p> <p>4 THE WITNESS: I didn't quite</p> <p>5 understand your question.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. Forget the question. We'll get --</p> <p>8 we'll walk you through it with documents in front</p> <p>9 of your face. We'll do it that way when we get to</p> <p>10 that.</p> <p>11 Okay. Are you an expert --</p> <p>12 rephrase.</p> <p>13 Do you believe that it's within your</p> <p>14 expertise to give an opinion as to whether or not</p> <p>15 ZHP should have thought about the question of</p> <p>16 whether or not the DMF could degrade during the</p> <p>17 zinc chloride process?</p> <p>18 A. You're asking whether my opinion is</p> <p>19 ZHP should have thought of this degradation as a</p> <p>20 potential? You're asking that?</p> <p>21 Q. You believe -- you believe that</p> <p>22 question, that you're an expert in answering that</p> <p>23 question?</p> <p>24 A. I'm sorry. I don't think I clearly</p>
<p style="text-align: right;">Page 95</p> <p>1 could degrade potentially in the zinc chloride</p> <p>2 process? Did they even look at that question at</p> <p>3 all? Do you know? Yes or no.</p> <p>4 A. Well, I -- I cannot say yes or no</p> <p>5 because how can I read other people's mind, right?</p> <p>6 I can only judge based on my understanding is they</p> <p>7 don't know, and they did not expected to know.</p> <p>8 Q. Based on everything you read --</p> <p>9 A. Right.</p> <p>10 Q. -- what is your understanding about</p> <p>11 whether or not ZHP even thought about the question</p> <p>12 of whether or not the DMF could degrade during the</p> <p>13 zinc chloride process?</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 form of the question.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. What is your understanding of</p> <p>18 whether they even thought about the question at</p> <p>19 all?</p> <p>20 A. My understanding or my feeling is</p> <p>21 they didn't.</p> <p>22 Q. Your opinion is, if they thought</p> <p>23 about it, that you don't think they would have</p> <p>24 found out information that they later found out,</p>	<p style="text-align: right;">Page 97</p> <p>1 understand what you're asking because there's a</p> <p>2 couple of curves in the question itself.</p> <p>3 Q. You're holding ourself out as an</p> <p>4 expert in organic chemistry in this case, right?</p> <p>5 A. Yes.</p> <p>6 Q. In terms of what the chemists at a</p> <p>7 drug manufacturing company called ZHP should have</p> <p>8 thought about in performing their risk assessment</p> <p>9 for the zinc chloride process, is that within your</p> <p>10 expertise what questions they should have thought</p> <p>11 about in developing the process?</p> <p>12 A. Yes.</p> <p>13 Q. Okay. In your opinion, should ZHP's</p> <p>14 -- rephrase.</p> <p>15 In your opinion, should ZHP have at</p> <p>16 least thought about the question of whether or not</p> <p>17 DMF could introduce DMA into the zinc chloride</p> <p>18 process? Should they have considered the</p> <p>19 question?</p> <p>20 A. I don't think there's available</p> <p>21 information for them during the time when this</p> <p>22 chemistry was developed to -- to trigger that</p> <p>23 thought. But, again, I cannot speak for them, but</p> <p>24 that's my understanding. So there's -- there's</p>

<p style="text-align: right;">Page 98</p> <p>1 not enough to say that.</p> <p>2 Q. Is one of your opinions -- well,</p> <p>3 rephrase.</p> <p>4 Do you agree with me that the DMF</p> <p>5 was capable of degrading to form dimethylamine</p> <p>6 during the zinc chloride process? Yes or no.</p> <p>7 A. You ask me now?</p> <p>8 MR. BERNARDO: Wait, wait,</p> <p>9 wait.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. I'm asking you now. As you sit here</p> <p>12 right now, is the answer yes or no?</p> <p>13 MR. BERNARDO: Object to the</p> <p>14 form of the question. Vague.</p> <p>15 Go on, Dr. Xue.</p> <p>16 THE WITNESS: Right.</p> <p>17 If you ask me now after I</p> <p>18 involve in this case and reading this</p> <p>19 reaction like hundred times over the last</p> <p>20 month. So now, yes, I know.</p> <p>21 But we are not talk about the</p> <p>22 reaction happen right now, right? So I</p> <p>23 -- it's not also not talk. Maybe talk</p> <p>24 about ZHP when they try to develop this</p>	<p style="text-align: right;">Page 100</p> <p>1 already said, right? So they really have no</p> <p>2 reason to do so because they don't know. It could</p> <p>3 be a possible factor.</p> <p>4 Q. Well, Dr. Xue.</p> <p>5 A. Yes.</p> <p>6 Q. You've been telling me what they</p> <p>7 could or could not have known. I haven't asked</p> <p>8 you that question.</p> <p>9 I asked you if they did certain</p> <p>10 tests. So I would appreciate if you could limit</p> <p>11 your answers to the actual questions I ask instead</p> <p>12 of talking about things I'm not asking you about.</p> <p>13 Can you do that for me, please?</p> <p>14 MR. BERNARDO: And I would</p> <p>15 appreciate if your questions and your</p> <p>16 comments to the witness were not</p> <p>17 argumentative and if you would conduct</p> <p>18 yourself appropriately for an expert</p> <p>19 deposition.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. Can we do that, Dr. Xue?</p> <p>22 I would appreciate it if I ask a</p> <p>23 question about one thing if you don't talk about</p> <p>24 another thing. It would make the deposition go</p>
<p style="text-align: right;">Page 99</p> <p>1 in 2013 or 2014, that's a totally</p> <p>2 different situation.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. Did ZHP do any lab scale testing to</p> <p>5 replicate the temperatures the zinc chloride</p> <p>6 process would subject the DMF to in order to see</p> <p>7 whether or not DMA would form under those</p> <p>8 conditions?</p> <p>9 I'm just asking if they did any</p> <p>10 tests of that question when they developed the</p> <p>11 zinc chloride process. Yes or no.</p> <p>12 A. Well, again, there are things I</p> <p>13 read. If you want to discuss about a specific</p> <p>14 document, I prefer if you can put it up so we can</p> <p>15 discuss specifically.</p> <p>16 But if you ask me off my head</p> <p>17 whether they did a lab scale testing of -- they</p> <p>18 did lab scale quality control when they actually</p> <p>19 do the risk assessment. When they try to make the</p> <p>20 switch from the -- the previous -- I think it's</p> <p>21 TEA process with quenching to the zinc chloride.</p> <p>22 They did this assessment on the lab</p> <p>23 scale. I don't think they did this -- this --</p> <p>24 this test about whether DMA is there. Because I</p>	<p style="text-align: right;">Page 101</p> <p>1 smoother, okay?</p> <p>2 A. I'll try my best.</p> <p>3 Q. Thank you.</p> <p>4 Based on your review of the</p> <p>5 materials, you saw no evidence that ZHP actually</p> <p>6 did any tests, whether in the lab or at any other</p> <p>7 stage, where they ever actually tested to see if</p> <p>8 they subjected the DMF to the conditions it would</p> <p>9 be subjected to in the zinc chloride process</p> <p>10 whether or not it would degrade to give off</p> <p>11 dimethylamine.</p> <p>12 No such test was performed to your</p> <p>13 knowledge, correct?</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 form of the question. Asked and</p> <p>16 answered.</p> <p>17 Go ahead.</p> <p>18 THE WITNESS: As I said, in</p> <p>19 test, they didn't test the formation of</p> <p>20 DMA during the process during the</p> <p>21 development. That's because at that</p> <p>22 time, they don't know that they need to</p> <p>23 test that.</p> <p>24 BY MR. SLATER:</p>

<p style="text-align: right;">Page 102</p> <p>1 Q. Why did you throw in the last part 2 "that's because" when I didn't ask you about the 3 reason? I just asked whether they did the test or 4 not. So why did you throw in the other part? 5 A. I just want amore complete answer. 6 Q. But I didn't ask that question. So, 7 I mean, the more complete answer could be 8 everything you know. I just would appreciate if 9 you would limit your answers to the question I 10 ask. 11 MR. BERNARDO: Object. 12 THE WITNESS: I will keep 13 that in mind. Thank you. 14 BY MR. SLATER: 15 Q. If I understand your opinion, it's 16 that ZHP -- withdrawn. 17 In your opinion -- well, rephrase. 18 Is it your opinion that the only way 19 that the dimethylamine was -- was introduced to 20 the zinc chloride process was during the tetrazole 21 step when the heating was to 135 plus or minus 22 degrees Celsius? Is that when you believe the DMA 23 was introduced to the process? 24 A. When I look at the process, right?</p>	<p style="text-align: right;">Page 104</p> <p>1 around this problem to be performed, and 2 then that will give us a clear answer for 3 this question. 4 BY MR. SLATER: 5 Q. Do you have an opinion, as you sit 6 here right now, as to how the DMA was introduced 7 to the zinc chloride process? 8 This is a yes-or-no question. I 9 want to know if you have an opinion as to how it 10 happened. 11 MR. BERNARDO: Object to the 12 form of the question. 13 BY MR. SLATER: 14 Q. I just want to know if you have the 15 opinion. I'm not even asking what the opinion is. 16 Yes or no. Do you have an opinion 17 on that? 18 A. You ask me for opinion that DMA was 19 formed during the zinc chloride -- 20 Q. Not what I asked you, Doctor. You 21 need to listen to my question, please. 22 Do you have an opinion as to how the 23 DMA was introduced to the zinc chloride process? 24 Yes or no.</p>
<p style="text-align: right;">Page 103</p> <p>1 So that's something the plaintiffs' expert point 2 out. So I was just focused on that step and then 3 look at this step. 4 Q. Is that your opinion? 5 MR. BERNARDO: He's finishing 6 his answer, Adam, please. 7 THE WITNESS: I'm trying to 8 finish. If you can let me. Thank you. 9 Right. So I -- I look at 10 the -- the opinion from the -- the expert 11 from the plaintiff side and that's what 12 they were saying. So I tried to address 13 that and I tried to. 14 Right now based on all the 15 result already out there, yes. So I feel 16 the degradation from DMF is likely the 17 reason why. 18 Although I, as a scientist, 19 before reading the study from FDA labs or 20 ZHP or other companies, they have a 21 conclusion. I won't just say for sure 22 this will be the cause or that will be 23 cause because I'm, you know, this must be 24 -- there must be some scientific studies</p>	<p style="text-align: right;">Page 105</p> <p>1 A. I do. 2 Q. In simple terms, what is your 3 opinion as how the DMA was introduced to the zinc 4 chloride process? 5 A. The DMA can actually form from 6 different ways. 7 Q. I'm asking what your opinion is to a 8 reasonable -- 9 A. Right. 10 Q. -- degree of scientific certainty as 11 to how it happened in the zinc chloride process. 12 If you have that opinion, tell me. 13 If you don't know or you're not sure, you can say, 14 "I don't know" or "I'm not sure." 15 A. Well, degradation of DMF is one of 16 those, right? And there's other conditions 17 involved in the tetrazole formation step. The 18 zinc chloride. I don't know, right. So there 19 might be. Also other factors. 20 As I said, that's my feeling. 21 Because now we know DMA is in there and nobody 22 does any project to figure out how, right? So my 23 opinion is I said, yes, degradation from DMF is 24 suspicious.</p>

<p style="text-align: right;">Page 106</p> <p>1 Q. Is it your understanding that nobody 2 has tried to figure out how the DMA got into the 3 zinc chloride process? 4 MR. BERNARDO: Object to the 5 form of the question. 6 THE WITNESS: Are you asking 7 me my understanding is nobody means? 8 BY MR. SLATER: 9 Q. Doctor, you just said to me nobody 10 tried to figure it out. I'm literally repeating 11 your answer to you. 12 A. No. At this -- well, I haven't seen 13 any result from any publication or announcement 14 saying what is the exact reason that dimethylamine 15 was formed. I haven't seen that. 16 Q. Okay. 17 A. If you have a document, I'd like to 18 see that document. 19 Q. Well, what I'm trying to figure out 20 is what you know to form -- to support the 21 opinions you've given in this case. My goal right 22 now is not to educate you and get new opinions. 23 So I'm trying to figure out what you 24 know now. Okay?</p>	<p style="text-align: right;">Page 108</p> <p>1 I use the word "suspect" that can be 2 actually happen. 3 I also said that the other 4 conditions involving the reaction can 5 actually contribute, which nobody did 6 research yet. Until we have some sort of 7 publication on this case, I don't think I 8 can agree with anybody's speculation. 9 BY MR. SLATER: 10 Q. So I'm going to come back to the 11 question I asked you a few minutes ago because 12 you're telling me there's possibilities, but 13 you're not sure which one happened. 14 What I need to know is: Do you hold 15 an opinion now to a reasonable degree of 16 scientific certainty where you can say more likely 17 than not the DMA was introduced to the zinc 18 chloride process through this means? 19 Do you have an opinion as to that? 20 Not it could be a bunch of things, 21 but do you have an opinion as to what it was that 22 actually caused the DMA to be introduced to the 23 zinc chloride process? Yes or no. 24 A. I don't have a specific reason to</p>
<p style="text-align: right;">Page 107</p> <p>1 A. What I know now is -- is -- is 2 during the zinc chloride process, somehow during 3 that zinc -- during that tetrazole formation step, 4 there are dimethylamine formed. I don't know 5 exactly because, again, I'm a scientist. Until I 6 see a definite experimental evidence, I cannot see 7 anything. I suspect that's the degradation of DMF 8 maybe with some sort of assistance from other 9 reagent used in combination. I don't know, but 10 that's my -- my feeling at this moment. 11 Q. So you agree with me that DMF was 12 capable of degrading at the temperatures it was 13 exposed to during the zinc chloride process and 14 forming dimethylamine, correct? 15 MR. BERNARDO: Object to the 16 form of the question. 17 BY MR. SLATER: 18 Q. You agree with that as you sit here 19 right now, correct? 20 MR. BERNARDO: Object. 21 THE WITNESS: I don't agree. 22 I think I made it clear. 23 This is one of the 24 possibilities. It's a chance, I suspect.</p>	<p style="text-align: right;">Page 109</p> <p>1 say exactly this must be the road that DMA has 2 been formed during this step. I don't have that. 3 Because how can I have something which no research 4 has been done on this? 5 Q. All right. Let's go back to the 6 deviation investigation report that we marked 7 earlier. 8 What did we mark it as? 9 A. Which? Can you remind me the number 10 again? 11 Q. Yeah, I can. It's Exhibit -- 12 MR. BERNARDO: 5? 13 MR. SLATER: It's Exhibit 5. 14 Exactly. 15 MR. BERNARDO: Wow. 16 BY MR. SLATER: 17 Q. And let's go to -- 18 A. So can you remind me the number of 19 the file? Number? 20 MR. BERNARDO: It's Exhibit 5, 21 Dr. Xue. 22 THE WITNESS: Yeah, Exhibit 23 file number 3. 24 MR. BERNARDO: Oh, I don't.</p>

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1 THE WITNESS: On my list.
2 Can somebody?
3 BY MR. SLATER:
4 Q. Let's go in that document to page
5 170.
6 MR. BERNARDO: Adam, one
7 second. He's asking -- I'm trying to
8 look where -- he's trying to pull it up
9 where --
10 THE WITNESS: 5 exhibit?
11 Which one?
12 BY MR. SLATER:
13 Q. Exhibit 5, the deviation
14 investigation report.
15 A. Number 5?
16 Okay. I'm on that report. Thank
17 you.
18 Q. Let's go to page 9 of 236 within
19 that report.
20 A. To you said page 9 of 236?
21 Q. Yeah. You see at the top right
22 there? You see -- see on the screen, Doctor?
23 Look on the screen.
24 A. Oh.

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1 Q. You see page 9?
2 A. Okay. Thank you for highlighting me
3 that. Let me --
4 Q. You can also look at it on your
5 screen. You can do whatever you want.
6 A. Okay.
7 Q. Do you see the page I'm asking you
8 about, page 9 of 236?
9 A. I am.
10 Q. And you can see that on page 9 of
11 236, ZHP conducted lab scale trials.
12 You see that in the middle of the
13 page? It says:
14 "For further confirmation, the
15 following lab scale trials were designed and
16 performed to verify the concluded formation
17 mechanism of NDMA."
18 Do you see that?
19 A. I see that section and the Table
20 3-1.
21 Q. And it says:
22 "The amount of NDMA formed by
23 quenching under different temperatures is shown in
24 the table below."

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1 Do you see that?
2 A. I see that table, the conditions.
3 Q. And you see that they subjected the
4 DMF plus zinc chloride to react at 135 degrees
5 Celsius for 20 hours, and they talk about what
6 they did and eventually added the sodium nitrite
7 later.
8 Do you see that?
9 A. Yes.
10 Q. And you see the NDMA in parts per
11 million that was produced by these various
12 experiments?
13 A. There's a column called "NDMA
14 (ppm)," right. That's the column you talk about,
15 right?
16 Q. Right.
17 A. Okay.
18 Q. Right. Have you ever seen this page
19 before right now?
20 A. Yeah, I don't remember exactly
21 whether I see this page, but, yeah, I do read this
22 document before.
23 Q. I didn't see anything in your report
24 where you talked about the fact that ZHP actually

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1 performed lab scale trials where they proved that
2 under the conditions of the zinc chloride process,
3 NDMA would form from the DMF and the sodium
4 nitrite.
5 Do you see that?
6 Let me withdraw it and ask it again.
7 I don't see any discussion in your
8 report about the lab scale trials that were
9 performed by ZHP to prove that the NDMA could form
10 under the conditions of the zinc chloride process.
11 You don't talk about that in your
12 report, right?
13 MR. BERNARDO: Object to the
14 form of the question. Assumes facts.
15 THE WITNESS: I didn't talk
16 about that in my report because I thought
17 that's -- that's the best of fact, right?
18 So we already by the year of
19 2018 knew that these impurity can
20 actually form as a side product in the
21 reaction that they try to do for the
22 tetrazole formation. I think that's the
23 fact, right?
24 So I didn't know that I have

<p style="text-align: right;">Page 114</p> <p>1 to repeat what the fact is. And these 2 experiment was this period is to try to 3 figure out, as you highlight here, at 4 different conditions how much of NDMA can 5 form. 6 I think that that's kind of a 7 backward looking back from 2018. Say, 8 oh, now we know under the condition that 9 I perform the tetrazole formation 10 reaction, there is. That's a conclusion 11 already draw, and then they look back to 12 try to change the condition to figure out 13 which parameter maybe play a bigger role. 14 And it looks like to me all 15 the six entries they actually did, they 16 all form some, to some extent, in ppm 17 value percentage some -- some DMAs. 18 So I don't see why there's any 19 conflict here. So I -- I don't see why I 20 should actually include this citing this 21 table because that's already be the fact 22 that by the time when they actually look 23 back. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 116</p> <p>1 topic, we have to know what we talk about, right? 2 So this is in 2018 when the whole 3 thing showed up. Everybody understand, including 4 myself now, right? So this reaction could 5 actually lead to this impurity. Nobody want that. 6 ZHP didn't want it. Nobody want that, but it 7 happen. 8 Now, when we look back to figure, 9 oh, what is the cause? Why this actually happen? 10 They did this whole bunch of analysis. 11 Actually, in my lab, we do this as 12 well, right? So we cannot design a project that 13 goes just like you design. Unfortunately, science 14 is not like that, right? 15 So happens a lot of time, if not all 16 the project, that at the end or on the way you 17 will find out the reaction didn't go like you will 18 happen, right? So you isolate and characterize 19 and find, okay, there is impurity, unfortunately, 20 formed. It's not something designed. It cost me 21 time and money, but we need to look back to see 22 how, what is the reason cause this. 23 So to do that, the general exercise 24 what I do, a lot of my colleagues, everybody in my</p>
<p style="text-align: right;">Page 115</p> <p>1 Q. My question is very simple. 2 Nowhere in your report do you talk 3 about the fact that ZHP did lab scale testing to 4 prove that the DMF could degrade, form DMA, and 5 then the sodium nitrite could combine with that to 6 create NDMA. 7 You don't discuss the fact that they 8 did those tests in your report, correct? 9 I'm not asking why you didn't do it. 10 I just want to confirm you didn't do it, right? 11 MR. BERNARDO: Objection. 12 THE WITNESS: Well, I do -- 13 MR. BERNARDO: Wait, wait, 14 wait, Dr. Xue. 15 Object to the form of the 16 question. Argumentative. 17 Go ahead, Dr. Xue. 18 BY MR. SLATER: 19 Q. I just want to know. Did I miss 20 it? Is it in your report or not? Just please. 21 It's a yes-or-no question. 22 A. You missed because it's a time 23 matter, right? It just like you run reaction, you 24 have to know the parameter. Here we discuss the</p>	<p style="text-align: right;">Page 117</p> <p>1 lab they also do is just to -- to see, okay, then 2 let's see what is a possible reason to cause this. 3 I believe this is what they did, right? 4 So, you know, I really don't see why 5 I should actually include this piece in there. So 6 what I want to prove? I don't see a point that 7 can actually bring to me, right? 8 We are not talk about, right, if you 9 tell me, okay, this is a table that ZHP or anybody 10 at ZHP they actually did in 20 -- in 2007 or 2010 11 even, right? So they know this already. That's 12 totally a different story, right? But we not talk 13 about that every. 14 I hope I address your question. 15 Q. Okay. Simple yes-or-no question. 16 Did you talk about ZHP's testing as 17 shown on page 9 of this deviation investigation 18 report in your report? Yes or no. 19 I just want to know if you talked 20 about it or not. 21 MR. BERNARDO: Dr. Xue, please 22 listen to Mr. Slater's question, right? 23 THE WITNESS: I didn't talk 24 about this experiment specifically in my</p>

<p style="text-align: right;">Page 118</p> <p>1 report.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. In fact, you didn't talk about any</p> <p>4 experiments performed by ZHP in your report,</p> <p>5 correct?</p> <p>6 A. So if I understand your question,</p> <p>7 you are asking do I mention any experiments ZHP</p> <p>8 performed in my report? That was your question,</p> <p>9 right?</p> <p>10 Q. Right. Yes-or-no question.</p> <p>11 A. I mentioned everything. If you read</p> <p>12 my report you said, right? I mention every</p> <p>13 single, all four of their processes. Every step I</p> <p>14 actually have joined all those reaction in my</p> <p>15 report. I mention every reaction they perform,</p> <p>16 how they do it, and what the conditions are. When</p> <p>17 they actually make any change, what kind of</p> <p>18 parameter they actually change they follow. They</p> <p>19 perform all these testings. I mention that.</p> <p>20 If you ask me whether these six</p> <p>21 reaction you show in this table right now? I</p> <p>22 didn't mention that. As I explain to you just</p> <p>23 now, I don't see why I should mention that in my</p> <p>24 report.</p>	<p style="text-align: right;">Page 120</p> <p>1 let me ask you this.</p> <p>2 Did you consider -- I don't want to</p> <p>3 do it that way, actually.</p> <p>4 Did ZHP take into consideration</p> <p>5 whether or not DMA, which is dimethylamine, could</p> <p>6 be an impurity of commercially purchased DMF such</p> <p>7 that they could introduce DMA into the zinc</p> <p>8 chloride process as an impurity when they put the</p> <p>9 DMF into the process? Did they consider that</p> <p>10 possibility?</p> <p>11 MR. BERNARDO: Object to the</p> <p>12 form of the question. Compound.</p> <p>13 Go ahead.</p> <p>14 THE WITNESS: So now we are</p> <p>15 changing to from formation from a</p> <p>16 degradation to -- to you imply there's a</p> <p>17 contamination already before they</p> <p>18 actually perform the reaction in common</p> <p>19 with the DMF? That what -- that's what</p> <p>20 you refer to?</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Did ZHP consider that possibility,</p> <p>23 to your knowledge?</p> <p>24 A. To my knowledge, I don't think they</p>
<p style="text-align: right;">Page 119</p> <p>1 Q. So if I understand your opinion, ZHP</p> <p>2 proved after the fact that the DMF could degrade</p> <p>3 to give off dimethylamine, but there's no way that</p> <p>4 they would have known that before they developed</p> <p>5 the process or while they used the process. So</p> <p>6 they were never on notice that DMA might be</p> <p>7 introduced to the zinc chloride process; is that</p> <p>8 correct?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question and the</p> <p>11 characterization of his testimony.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. Is that your opinion?</p> <p>14 MR. BERNARDO: Go ahead.</p> <p>15 THE WITNESS: So I'm here</p> <p>16 trying to address the -- the expert from</p> <p>17 the plaintiff side, right?</p> <p>18 So my opinion, I think, is</p> <p>19 very clear I mention about these. They</p> <p>20 have no -- they don't know and they have</p> <p>21 not reasonably be able to expect to know</p> <p>22 these are actually can trigger the issue.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Did ZHP consider the fact -- well,</p>	<p style="text-align: right;">Page 121</p> <p>1 did.</p> <p>2 Q. That's all I asked.</p> <p>3 A. Thank you. I got one.</p> <p>4 Q. In forming your opinions, did you</p> <p>5 consider the possibility that DMA could have been</p> <p>6 introduced to the zinc chloride process as an</p> <p>7 impurity of the DMF?</p> <p>8 A. You're asking me when I formed my</p> <p>9 opinion whether I considered contamination of DMF</p> <p>10 by DMA? You ask me about that? I just want to</p> <p>11 confirm that's what the question you're asking.</p> <p>12 Q. Yes. When you formed your opinion,</p> <p>13 did you consider the possibility that DMA could be</p> <p>14 an impurity of commercially purchased DMF and be</p> <p>15 introduced to the zinc chloride process as an</p> <p>16 impurity of the DMF?</p> <p>17 A. Right.</p> <p>18 Q. Did you consider that possibility?</p> <p>19 A. Right. So when I --</p> <p>20 Q. It's a yes-or-no question. I just</p> <p>21 want to know if you considered that possibility or</p> <p>22 not. Yes or no.</p> <p>23 MR. BERNARDO: Objection.</p> <p>24 THE WITNESS: When I formed</p>

<p style="text-align: right;">Page 122</p> <p>1 my opinion, I mostly address what the --</p> <p>2 the expert from the plaintiff side,</p> <p>3 right? So I don't recall they actually</p> <p>4 raise this in their report. That's the</p> <p>5 reason why when I formed my opinion, I</p> <p>6 didn't really trying to include this</p> <p>7 section or this study, this discussion in</p> <p>8 my report.</p> <p>9 I think so far the only --</p> <p>10 because there's so many documents, right?</p> <p>11 But the only document that I can -- I can</p> <p>12 recall that -- that sort of addressed</p> <p>13 this was, I think during the root cause</p> <p>14 study, ZHP did some sort of analysis of</p> <p>15 the DMF solvent they use in their</p> <p>16 processes.</p> <p>17 They found the, you know --</p> <p>18 I'm not regulatory science, right,</p> <p>19 scientist, but I know they found the --</p> <p>20 the grade of the DMF they used was -- was</p> <p>21 good. So they didn't actually find high</p> <p>22 ppm. I believe both DMA and DEA was --</p> <p>23 was way below the bar. I don't</p> <p>24 remember -- recall the specific numbers.</p>	<p style="text-align: right;">Page 124</p> <p>1 know because I can -- I cannot have</p> <p>2 know -- any reason to know whether ZHP</p> <p>3 know by then.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. You don't know. That's fine. It's</p> <p>6 okay. Based on everything you read, you don't</p> <p>7 know. That's your answer. It's fine.</p> <p>8 A. Yeah, I hope I can offer something.</p> <p>9 That's why.</p> <p>10 MR. SLATER: Let's -- let's</p> <p>11 put this aside for a second and put up as</p> <p>12 exhibit -- what are we up to 6 or 7?</p> <p>13 All right. Let's put up as</p> <p>14 Exhibit 6 the World Health Organization</p> <p>15 publication from 2001 titled</p> <p>16 "N,N-Dimethylformamide."</p> <p>17 THE WITNESS: Are you putting</p> <p>18 it up?</p> <p>19 (Document marked for</p> <p>20 identification as Xue Exhibit 7.)</p> <p>21 BY MR. SLATER:</p> <p>22 Q. We're putting it into the thing so</p> <p>23 you can download it. We're going to put it on the</p> <p>24 screen. I'm going to show you one page.</p>
<p style="text-align: right;">Page 123</p> <p>1 So that's the only reason.</p> <p>2 That's the only avenues, and then I don't</p> <p>3 think any of -- I might be wrong, but I</p> <p>4 don't think I read any of the -- the</p> <p>5 report from the plaintiff side mention</p> <p>6 those. So I didn't just -- just went on</p> <p>7 to address that directly.</p> <p>8 So I disagree that they didn't</p> <p>9 do any study or they don't know.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. Did ZHP know that the DMF it was</p> <p>12 purchasing could have DMA as an impurity and that</p> <p>13 it could be introduced into the zinc chloride</p> <p>14 process as an impurity of the DMF?</p> <p>15 Did ZHP know that when they --</p> <p>16 A. Well, as I said --</p> <p>17 Q. -- developed and used that process?</p> <p>18 Yes or no.</p> <p>19 I just want to know. What do you</p> <p>20 know about that? Yes or no. Did they know?</p> <p>21 MR. BERNARDO: Object to the</p> <p>22 form of the question. Foundation.</p> <p>23 Go ahead.</p> <p>24 THE WITNESS: Well, I don't</p>	<p style="text-align: right;">Page 125</p> <p>1 So, first of all, are you familiar</p> <p>2 with this document? Have you seen this?</p> <p>3 A. I think I saw this before.</p> <p>4 Q. Okay. This would be scientifically</p> <p>5 knowable to somebody who was developing the zinc</p> <p>6 chloride process at ZHP, right?</p> <p>7 MR. BERNARDO: Object to the</p> <p>8 form of the question.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. This document would be available to</p> <p>11 somebody who's a chemist at ZHP, right?</p> <p>12 A. Well, as you just described, the</p> <p>13 document is available. I don't know whether ZHP</p> <p>14 has read that or not. I cannot speak for other</p> <p>15 people. I read this before. It is available as</p> <p>16 you described.</p> <p>17 Q. Let's go to page 5.</p> <p>18 A. Okay. 5 of the document, right?</p> <p>19 Q. Yep. It's right there on the</p> <p>20 screen. Paragraph 2. Or not. Rephrase.</p> <p>21 Looking at page 5 of this</p> <p>22 publication, Section 2 titled "Identity and</p> <p>23 Physical/Chemical Properties" in the bottom,</p> <p>24 right.</p>

<p style="text-align: right;">Page 126</p> <p>1 Do you see that?</p> <p>2 It's on the screen, Doctor. It's</p> <p>3 right in front of you on the screen.</p> <p>4 Do you see it?</p> <p>5 A. Yeah. Yeah. Yeah. I mean, I'm</p> <p>6 sorry. I was looking at my -- my own trying to.</p> <p>7 Yeah, go ahead.</p> <p>8 Q. And there's a paragraph that talks</p> <p>9 about N,N-Dimethylformamide.</p> <p>10 Do you see that first paragraph?</p> <p>11 A. The second last paragraph from</p> <p>12 the -- on the right column, right?</p> <p>13 Q. Correct.</p> <p>14 A. Okay. I saw that.</p> <p>15 Q. The last sentence of that paragraph</p> <p>16 says:</p> <p>17 "DMF sold commercially contains</p> <p>18 trace amounts of methanol, water, formic acid, and</p> <p>19 dimethylamine." And there's a citation to 1994.</p> <p>20 Do you see what I just read?</p> <p>21 A. I saw what you just read.</p> <p>22 Q. Before I just showed you that, were</p> <p>23 you aware that DMF sold commercially contains</p> <p>24 trace amounts of methanol, water, formic acid, and</p>	<p style="text-align: right;">Page 128</p> <p>1 small molecules can actually present in DMF, I</p> <p>2 don't know.</p> <p>3 Q. Okay. In forming your opinions in</p> <p>4 this case --</p> <p>5 A. Right.</p> <p>6 Q. -- did you consider the fact that</p> <p>7 DMF sold commercially contains trace amounts of</p> <p>8 dimethylamine such that DMA -- well, let me stop</p> <p>9 there. Let me ask it again.</p> <p>10 When you formed your opinion in this</p> <p>11 case, did you take into account the fact that DMF</p> <p>12 sold commercially contains trace amounts of</p> <p>13 dimethylamine?</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 form of the question. Compound. Asked</p> <p>16 and answered.</p> <p>17 Go ahead, Dr. Xue.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Just want to know if you considered</p> <p>20 that when you formed your opinions in this case.</p> <p>21 A. Well, when we buy or when we use any</p> <p>22 chemical in practice as a chemist, right? So you</p> <p>23 always rely on the -- on the certificate you got</p> <p>24 from the vendor, right?</p>
<p style="text-align: right;">Page 127</p> <p>1 dimethylamine? Did you know that before right</p> <p>2 now?</p> <p>3 A. Are you -- if you ask me</p> <p>4 specifically of these four substance -- methanol,</p> <p>5 water, formic acid, and dimethylamine -- do I know</p> <p>6 whether these are the four contamination that can</p> <p>7 possibly contains in the -- in the DMF sold</p> <p>8 commercially, I probably don't know the four off</p> <p>9 my head. But as a --</p> <p>10 Q. Did you know -- go ahead.</p> <p>11 A. Sorry. Can I -- can I go ahead?</p> <p>12 Yeah.</p> <p>13 But as an organic chemist, right, we</p> <p>14 buy solvents like DMF or other solvent all the</p> <p>15 time, right? So they always have a certificate</p> <p>16 come along with it. So that's where we actually</p> <p>17 go for it.</p> <p>18 We -- we usually, like my lab, if we</p> <p>19 want a 99.9 percent, so we actually trust what the</p> <p>20 vendor told us and we read the -- we call it a</p> <p>21 Safety Data Sheet to actually learn this</p> <p>22 information.</p> <p>23 But if you ask me whether I know</p> <p>24 this particular sentence or these four specific</p>	<p style="text-align: right;">Page 129</p> <p>1 So this sentence by reading says</p> <p>2 "sold commercially contains trace amount" these.</p> <p>3 First of all, trace amount is a very vague. Like</p> <p>4 1 ppm or .001 ppm of each, that should be listed</p> <p>5 specifically for each one of the chemicals that</p> <p>6 you order.</p> <p>7 So this is just, I think, is a</p> <p>8 summary from the WHO. That really does not tell</p> <p>9 you a specific product for me. Because if I'm</p> <p>10 doing my research running my reaction, if I want</p> <p>11 to buy something that I care, I have to go</p> <p>12 specifically to that website and downloading the</p> <p>13 corresponding data sheet or called Safety Data</p> <p>14 Sheet to -- to read what exactly in there.</p> <p>15 So I don't take for granted that</p> <p>16 this is the four compound that must be contained</p> <p>17 in my DMF and, again, trace is a very vague number</p> <p>18 they will not use.</p> <p>19 Q. Doctor.</p> <p>20 A. Yes.</p> <p>21 Q. When you formed your opinion, did</p> <p>22 you take into account the possibility that the DMA</p> <p>23 was introduced into the zinc chloride process as</p> <p>24 an impurity or contaminant of the commercially</p>

<p style="text-align: right;">Page 130</p> <p>1 purchased DMF that was used? Yes or no.</p> <p>2 A. I didn't because ZHP showed during</p> <p>3 their study their DMF doesn't contain</p> <p>4 dimethylamine.</p> <p>5 Q. Okay. Now, next question.</p> <p>6 You said that you worked --</p> <p>7 A. But can I -- can I -- can I say</p> <p>8 something, too?</p> <p>9 Q. I asked you -- see, here's the</p> <p>10 problem, Doctor. I asked a simple question. You</p> <p>11 answered it. I don't know why you want to talk</p> <p>12 about something else.</p> <p>13 I didn't ask why. I'm not asking</p> <p>14 for an explanation. I'm never going to finish</p> <p>15 this deposition if you give me long stories about</p> <p>16 things I'm not asking about.</p> <p>17 A. I did not. I just want to point out</p> <p>18 one thing. While you're on this document, I was</p> <p>19 on the second screen I saw something. Can I raise</p> <p>20 that?</p> <p>21 Q. No. I'm not asking about something</p> <p>22 on the second screen. I asked you a simple</p> <p>23 question that's not even about this document at</p> <p>24 this point.</p>	<p style="text-align: right;">Page 132</p> <p>1 I didn't consider, one, because ZHP</p> <p>2 did the root cause study to show that their DMF</p> <p>3 didn't contain, and they have a specific number</p> <p>4 listed. They are not -- they are below 10 ppm,</p> <p>5 but they didn't do any.</p> <p>6 And plus, as I already mentioned,</p> <p>7 the expert from the plaintiff side during their --</p> <p>8 during their -- in their opinions or in their</p> <p>9 writing the report, they didn't address this. So</p> <p>10 that's why I didn't put it in there. That's the</p> <p>11 only evidence I saw. So I didn't -- I didn't</p> <p>12 address that in my report.</p> <p>13 But you want me to -- to agree with</p> <p>14 you that, you know, I didn't consider this. I</p> <p>15 want to let you know the truth. That's what I --</p> <p>16 I actually put down.</p> <p>17 And just now before I can finish,</p> <p>18 you take down that PowerPoint or not -- that</p> <p>19 document. I think it's not quite fair because I</p> <p>20 really just now see something.</p> <p>21 I mean, it's actually the page right</p> <p>22 next to that page that says actually the</p> <p>23 temperatures in excess of 350 degrees C are</p> <p>24 required for DMF to decompose into carbon monoxide</p>
<p style="text-align: right;">Page 131</p> <p>1 A. But you don't allow me to -- to</p> <p>2 raise that point? That's what you're saying?</p> <p>3 Q. I want an answer to my question, and</p> <p>4 you answered. You're not answering my question.</p> <p>5 My question -- let's take this down off the screen</p> <p>6 because I'm not even asking about this document.</p> <p>7 When you formed your opinions, did</p> <p>8 you take into account the possibility that the DMA</p> <p>9 was introduced to the zinc chloride process as a</p> <p>10 preexisting impurity or contaminant of the</p> <p>11 commercially purchased DMF that was used?</p> <p>12 You already said you did not take</p> <p>13 that into account, correct?</p> <p>14 A. I didn't. I said -- what I said --</p> <p>15 Q. That's all I asked. I just wanted</p> <p>16 to know if you took it --</p> <p>17 A. Can I explain?</p> <p>18 Q. -- into account, and you said no.</p> <p>19 A. Can I explain?</p> <p>20 Q. I understand why, but I don't -- I</p> <p>21 don't need an explanation. I'm going to go on to</p> <p>22 the next question now.</p> <p>23 A. No, that was not my -- my statement.</p> <p>24 That's not my testimony.</p>	<p style="text-align: right;">Page 133</p> <p>1 and dimethylamine. That's also on the same exact</p> <p>2 document that you just showed me. I think I have</p> <p>3 the right to point it out.</p> <p>4 So if we all agree, WHO is -- is out</p> <p>5 there and it's up there. Everybody should</p> <p>6 actually respect the WHO. So I think we need also</p> <p>7 think about WHO in their same document. If you</p> <p>8 put it up again on that -- on that file you just</p> <p>9 -- you just take down quickly.</p> <p>10 On page 6 of that document on the --</p> <p>11 on the left column on the top paragraph it says</p> <p>12 what I just read. "Temperatures in excess of 350</p> <p>13 degrees C." That's way, way above the condition</p> <p>14 that ZHP been using to perform their tetrazole</p> <p>15 formation reaction actually are required for DMF</p> <p>16 to decompose.</p> <p>17 So I want to -- I want to read that</p> <p>18 to you so you have a record. So that's something</p> <p>19 I want to point out.</p> <p>20 Q. You said something earlier.</p> <p>21 You said that you, as a -- as a</p> <p>22 chemist -- organic chemist, when you purchase</p> <p>23 substances, you look at the Material Safety Data</p> <p>24 Sheet.</p>

<p style="text-align: right;">Page 134</p> <p>1 Remember you said that?</p> <p>2 A. I usually do.</p> <p>3 Q. Are you familiar what a Certificate</p> <p>4 of Analysis is?</p> <p>5 A. I don't know off my head what</p> <p>6 Certificate of Analysis mean.</p> <p>7 Q. One of the things you said is, as an</p> <p>8 organic chemist, you should always rely on the</p> <p>9 certificate from the vendor as to what is in the</p> <p>10 substance you purchased, right?</p> <p>11 A. We -- we -- if we need information</p> <p>12 from there, like if I want to figure out the</p> <p>13 decomposition of DMF if I buy it, I will just go</p> <p>14 there to look. That's my -- that's my side. I</p> <p>15 usually do. I'm not saying everybody else should</p> <p>16 do the same. That's my practice. I teach my</p> <p>17 student the same way.</p> <p>18 Q. You would expect that the chemists</p> <p>19 at ZHP looked at the Certificate of Analysis to</p> <p>20 know the composition of the DMF they were</p> <p>21 purchasing to put into the zinc chloride process,</p> <p>22 right?</p> <p>23 A. Well, I cannot speculate for any</p> <p>24 other people than myself. I told you I do that.</p>	<p style="text-align: right;">Page 136</p> <p>1 Q. Yes or no. Did you or not?</p> <p>2 A. This is not a yes-or-no question.</p> <p>3 Can you let me finish?</p> <p>4 I told you early on, right, I was</p> <p>5 provided a lot of document. I also did my own</p> <p>6 research. So to go out to look for the data sheet</p> <p>7 was my own practice. Nobody provide this to me,</p> <p>8 and this is my routine exercise from -- for</p> <p>9 anything that I do.</p> <p>10 Q. Right.</p> <p>11 Did you do that here?</p> <p>12 A. I'm sorry. For which one?</p> <p>13 Q. Did you -- did you do any research</p> <p>14 to see what the Certificate of Analysis or the</p> <p>15 Material Safety Data Sheet or any information from</p> <p>16 the manufacturers of the DMF might have said about</p> <p>17 the contents of the DMF that was purchased by ZHP?</p> <p>18 Did you do any research on that?</p> <p>19 Yes or no.</p> <p>20 A. I did research myself to see what's</p> <p>21 available for DMF from the site that I purchase</p> <p>22 DMF. I don't know. I have no reason to know what</p> <p>23 ZHP has been purchased from. So I --</p> <p>24 Q. Is that -- is that in your reliance</p>
<p style="text-align: right;">Page 135</p> <p>1 Q. You have no opinion on that?</p> <p>2 A. Well, my opinion is I do that and my</p> <p>3 student in my lab, they all do that because I</p> <p>4 advise them to do so. I -- I cannot force other</p> <p>5 people to do the same way as I do.</p> <p>6 Q. Do you have an opinion as to whether</p> <p>7 the chemists at ZHP should have looked at the</p> <p>8 Certificate of Analysis for the DMF that they</p> <p>9 purchased for use in the zinc chloride process?</p> <p>10 I just want to know if you have an</p> <p>11 opinion on that or not. If you, you do. If you</p> <p>12 don't, you can say, "I don't have an opinion."</p> <p>13 A. I don't know what other people do.</p> <p>14 Q. Have you seen any Certificates of</p> <p>15 Analysis or Material Safety Data Sheets regarding</p> <p>16 the DMF or any of the other substances that were</p> <p>17 used in the zinc chloride process or the TEA with</p> <p>18 sodium nitrite quenching process?</p> <p>19 A. You ask me if I went in to look at</p> <p>20 the data sheet?</p> <p>21 Q. I'm asking if that was provided to</p> <p>22 you, if it's one of the materials you reviewed in</p> <p>23 forming your opinions in this case.</p> <p>24 A. Well, I --</p>	<p style="text-align: right;">Page 137</p> <p>1 list? Did you list that you did that research and</p> <p>2 what you found when you looked at your supplier's</p> <p>3 website on DMF?</p> <p>4 MR. BERNARDO: Object to the</p> <p>5 form of the question. Vague.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. I just want to know.</p> <p>8 Did you disclose it in your report</p> <p>9 or on your reliance list? Yes or no.</p> <p>10 MR. BERNARDO: Object to</p> <p>11 the --</p> <p>12 THE WITNESS: My reliance list</p> <p>13 has so many things. I disclose</p> <p>14 everything that is provide to me from the</p> <p>15 counsel. I disclose everything that I</p> <p>16 use to form my opinion.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. Did you disclose everything you</p> <p>19 found --</p> <p>20 A. If you push me to the corner --</p> <p>21 Q. -- in your report?</p> <p>22 A. Well, if you push me to the corner</p> <p>23 like this to say what I disclose exactly let me</p> <p>24 memorize at this moment everything, I don't think</p>

<p style="text-align: right;">Page 138</p> <p>1 is fair.</p> <p>2 Q. Doctor, I didn't ask you to disclose</p> <p>3 everything to me right now.</p> <p>4 I'm asking you. You just told me</p> <p>5 you did research on the website of your DMF</p> <p>6 supplier for your lab.</p> <p>7 A. Right.</p> <p>8 Q. Did you do that in connection with</p> <p>9 this case?</p> <p>10 A. I did search DMF.</p> <p>11 Q. What did you find?</p> <p>12 A. I'm sorry?</p> <p>13 Q. What did you find?</p> <p>14 A. I find a documentation that is</p> <p>15 called a Safety Data Sheet for my DMF search. I</p> <p>16 see the parameters that in there. I didn't look</p> <p>17 at every detail, but I did find in there they also</p> <p>18 mention the degradation temperature is 350</p> <p>19 degrees C.</p> <p>20 Q. Did they talk about in that document</p> <p>21 the potential for impurities including</p> <p>22 dimethylamine?</p> <p>23 A. I don't remember those.</p> <p>24 Q. You don't remember.</p>	<p style="text-align: right;">Page 140</p> <p>1 Q. Okay.</p> <p>2 A. I may use some as my citations, may</p> <p>3 use others as citations. For that I choose, but I</p> <p>4 didn't hide anything.</p> <p>5 Q. Well, I didn't ask if you hid</p> <p>6 anything. I just asked if you mentioned it or</p> <p>7 listed it anywhere in your report.</p> <p>8 A. Well, as I mentioned to you then, I</p> <p>9 really off my head I don't recall all these</p> <p>10 details. I hope you don't push me to do that.</p> <p>11 Q. Let's look at -- let's go back to</p> <p>12 the deviation investigation report.</p> <p>13 A. Can you remind me the number again?</p> <p>14 Q. It's Exhibit 5, sir.</p> <p>15 A. Thank you so much.</p> <p>16 Q. Go to page 157 of 236.</p> <p>17 Looking at the bottom half of the</p> <p>18 page.</p> <p>19 A. Sorry. I'm -- I'm moving slower</p> <p>20 than you.</p> <p>21 Q. It's right on the screen. I mean,</p> <p>22 you can see it. It's right on the screen.</p> <p>23 A. I understand it's on the screen.</p> <p>24 I'm sorry. I also want to see that report, the</p>
<p style="text-align: right;">Page 139</p> <p>1 Did you look at the Certificate of</p> <p>2 Analysis for the contents of the DMF, which is</p> <p>3 something that would be different from the</p> <p>4 Material Safety Data Sheet? Did you look for that</p> <p>5 document?</p> <p>6 A. Honestly, I don't even know what the</p> <p>7 document is. If you have example, if you put it</p> <p>8 up, I will probably be --</p> <p>9 Q. No.</p> <p>10 A. -- report that.</p> <p>11 Q. Okay. Where -- so you did research.</p> <p>12 You looked at a website, and I just want to know.</p> <p>13 Where is that listed in your report</p> <p>14 or on your list of materials reviewed? Is that</p> <p>15 listed anywhere?</p> <p>16 The DMF supplier's website. I just</p> <p>17 want to know. Is it listed in your report or your</p> <p>18 reliance list?</p> <p>19 A. Well, I --</p> <p>20 Q. It's a yes-or-no question.</p> <p>21 A. I don't know at this moment. I say</p> <p>22 I never hide anything. If I consider everything,</p> <p>23 I put in the report or put in the list of</p> <p>24 consideration. I...</p>	<p style="text-align: right;">Page 141</p> <p>1 document on my own so I know what I'm reading. I</p> <p>2 don't want to make any mistake.</p> <p>3 Q. Scroll down a tiny bit just so we</p> <p>4 can see the middle of the page also. No, the</p> <p>5 other way.</p> <p>6 A. Are you talking about page 153?</p> <p>7 Q. 157.</p> <p>8 A. Oh, 7.</p> <p>9 Okay. 57 -- 157 of 236.</p> <p>10 Q. All right. So looking right at the</p> <p>11 middle of the page, it talks about "Discussion on</p> <p>12 Suppliers of DMF" and there's "Supplier</p> <p>13 Information."</p> <p>14 Do you see that?</p> <p>15 A. I can read there's supplier</p> <p>16 information there.</p> <p>17 Q. And the paragraph says:</p> <p>18 "Huahai has written procedure 'API</p> <p>19 Supplier Procedure of Raw Materials SMP-018.08' to</p> <p>20 regulate the selection, examination, assessment,</p> <p>21 evaluation and audit of suppliers. There had been</p> <p>22 five suppliers of DMF (correspond to two</p> <p>23 manufacturers) in Huahai since 2010. All of them</p> <p>24 meet the requirements of the procedure by</p>

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1 reviewing supplier information. The details are
2 in Table 4-32 as follows."
3 Do you see what I just read?
4 A. Yes, I did see the section that you
5 read.
6 Q. And if you look at the table below,
7 it lists the suppliers and the manufacturers of
8 the DMF.
9 Do you see that?
10 A. I see there's a Table 3 columns,
11 right? They talk about the suppliers,
12 manufacturer, and the approval dates. Yes.
13 Q. Okay. And you see one of the
14 companies is Shandong Hualu Hengsheng Chemicals
15 Company, Limited? Do you see that's one of the
16 manufacturers of the DMF that was used by ZHP?
17 A. I --
18 Q. In the Manufacturer column, if you
19 read the manufacturers' names, there's two
20 manufacturers. One of them is Shandong Hualu
21 Hengsheng Chemicals.
22 Do you see them?
23 A. You talk about the last one in the
24 column. Is that the --

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1 Q. It's the column that -- there's a
2 column that says "Manufacturer."
3 Do you see the column?
4 A. Right. I see within the column you
5 talk about the last row.
6 Q. Yes.
7 A. Okay. Yeah.
8 Q. If you go to the next page, you'll
9 see they're also listed there, too, okay? But
10 that's Shandong. I'm going to call them Shandong.
11 Okay?
12 A. So I --
13 Q. Doctor, I don't know what we're
14 doing. Let me -- let me do this.
15 Do you see one of the manufacturers
16 is Shandong Hualu --
17 A. Yes.
18 Q. -- Hengsheng Chemicals?
19 A. I do. You also talk about next
20 page, right?
21 Q. Forget that. Forget it. I'm asking
22 you to read that.
23 A. Okay. Yeah.
24 Q. You see Shandong is one of the

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1 manufacturers?
2 A. Based on reading, that is. Yes.
3 MR. SLATER: Okay. Let's put
4 up the Shandong document now.
5 I would -- I would like to --
6 well, do you have it all as one document?
7 Make it into one document and
8 let's put it up. Put up whatever you
9 have. I just want to move through this.
10 I'd rather have done it as
11 one, but we'll do it all. I just want to
12 move through this.
13 BY MR. SLATER:
14 Q. What we did, Doctor, is we went on
15 the Internet and we got the Certificate of
16 Analysis for Shandong's DMF.
17 And I'm just going to walk you
18 through what we did.
19 This is the website we went to.
20 Okay? This is Shandong's website.
21 A. I'm sorry. Are you talking about
22 the PDF you're showing me now?
23 Q. Yeah, this is Exhibit what?
24 A. It's written in Japanese and

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1 English?
2 Q. What I'm showing you is a website --
3 hold on.
4 All right, Doctor, we're going to
5 cut to the chase here. We're going to put up on
6 the screen. What exhibit number are we up to?
7 A. Number --
8 Q. I'm not asking you, Doctor. Sorry.
9 A. Sorry.
10 MR. SLATER: What exhibit is
11 this?
12 Okay. This is Exhibit 7.
13 (Document marked for
14 identification as Xue Exhibit 7.)
15 MR. SLATER: Two pages?
16 BY MR. SLATER:
17 Q. Doctor, on the screen is Exhibit 7.
18 It's a Certificate of Analysis that we obtained
19 for Shandong's DMF.
20 Do you see that on the screen?
21 MR. BERNARDO: I'm just going
22 to reserve my objection to this. I don't
23 have a copy of it to look at yet, but
24 just reserve. Go on.

<p style="text-align: right;">Page 146</p> <p>1 BY MR. SLATER:</p> <p>2 Q. Okay.</p> <p>3 A. Well, I can -- I can see the</p> <p>4 document. This, again, is also new to me. I</p> <p>5 haven't seen this document before.</p> <p>6 Q. Do you see that it has a list -- a</p> <p>7 list of specifications and results and shows that</p> <p>8 there's dimethylamine at 1 part per million in the</p> <p>9 DMF from Shandong?</p> <p>10 MR. BERNARDO: I object to the</p> <p>11 form of the question.</p> <p>12 And, Adam, can you just</p> <p>13 display so we all know what the date of</p> <p>14 this document is at least? I don't have</p> <p>15 a copy of it.</p> <p>16 MR. SLATER: I don't know the</p> <p>17 date of the document. I don't know what</p> <p>18 that is.</p> <p>19 MR. BERNARDO: You're asking</p> <p>20 the witness a question.</p> <p>21 MR. SLATER: Hey, I don't need</p> <p>22 to be laughed. Okay? So you want to do</p> <p>23 that, do that with somebody else.</p> <p>24 MR. BERNARDO: Okay. Adam,</p>	<p style="text-align: right;">Page 148</p> <p>1 MR. SLATER: So the answer is</p> <p>2 you don't want to answer whether you</p> <p>3 actually produced them. So nobody</p> <p>4 else --</p> <p>5 MR. BERNARDO: So the answer</p> <p>6 is that I'm not being deposed here, Adam.</p> <p>7 I'm simply asking for the date of the</p> <p>8 document that we're all looking at on the</p> <p>9 screen so I understand what we're looking</p> <p>10 at.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. I'm showing you a Certificate of</p> <p>13 Analysis from Shandong Hualu-Hengsheng Chemical</p> <p>14 Co. for dimethylformamide shows that it has</p> <p>15 dimethylamine --</p> <p>16 MR. BERNARDO: Objection.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. -- consistent with that publication</p> <p>19 we showed you before saying that dimethylamine is</p> <p>20 an impurity of DMF.</p> <p>21 Do you see that on the screen?</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. Vague.</p> <p>24 THE WITNESS: I'm sorry.</p>
<p style="text-align: right;">Page 147</p> <p>1 there's not an iota of laughter in what I</p> <p>2 said and you know that, and let's just --</p> <p>3 come on, Adam.</p> <p>4 MR. SLATER: I'm watching your</p> <p>5 face. I want to continue the deposition.</p> <p>6 You guys --</p> <p>7 MR. BERNARDO: I do, too, but</p> <p>8 don't comment and claim I'm laughing when</p> <p>9 I'm not.</p> <p>10 MR. SLATER: Hey, you're the</p> <p>11 one who asked my expert if he's seen the</p> <p>12 Certificates of Analysis for the DMF that</p> <p>13 to our knowledge was never produced by</p> <p>14 your client. Okay?</p> <p>15 MR. BERNARDO: Let's move on.</p> <p>16 MR. SLATER: Unless you want</p> <p>17 to make a representation that -- hey, do</p> <p>18 you want to tell us right now whether the</p> <p>19 Certificate of Analysis for the DMF were</p> <p>20 actually produced? Because our</p> <p>21 understanding is they weren't and we're</p> <p>22 not sure why.</p> <p>23 MR. BERNARDO: Okay. Let's</p> <p>24 move on and ask the witness.</p>	<p style="text-align: right;">Page 149</p> <p>1 The -- the -- on my screen says "Internet</p> <p>2 unstable." I really didn't. I only hear</p> <p>3 you said "DMF" at the end. I didn't hear</p> <p>4 the question at all. Can you please</p> <p>5 repeat your question?</p> <p>6 BY MR. SLATER:</p> <p>7 Q. Do you see on the Certificate of</p> <p>8 Analysis it shows that the DMF contains</p> <p>9 dimethylamine?</p> <p>10 MR. BERNARDO: Object to the</p> <p>11 form of the question. Vague.</p> <p>12 THE WITNESS: On the table</p> <p>13 that you show me on this document, which</p> <p>14 I've never seen before, there is entry a</p> <p>15 couple dimethylamine ppm.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Do you agree with me that the</p> <p>18 chemists at ZHP should have been aware that DMA</p> <p>19 can be an impurity or a contaminant of the DMF</p> <p>20 that they were using? Should have been aware of</p> <p>21 that possibility? Should they have thought about</p> <p>22 that?</p> <p>23 MR. BERNARDO: Object to the</p> <p>24 form of the question. Vague. Assumes</p>

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1 facts not in evidence.
 2 BY MR. SLATER:
 3 Q. Or do you have no opinion on that
 4 question?
 5 A. Well, first of all, this document,
 6 when did you get this document?
 7 Q. Doctor, I just asked you a question
 8 not about this document.
 9 A. Because this document is not very
 10 clear to me. So what --
 11 Q. Doctor, I didn't ask you about the
 12 document. So I'm not really sure why you're
 13 talking about it.
 14 Take it down.
 15 A. No. What date that you download
 16 this document. Is the document from --
 17 Q. The document was downloaded in the
 18 last few days.
 19 A. Okay. So -- so that means this is
 20 the --
 21 Q. You want to answer me? I don't know
 22 why you're talking to me about this because that's
 23 not what I asked you. I asked you a very direct
 24 question.

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1 A. I want -- I want to answer your
 2 question so that's why.
 3 Q. Okay. So let me ask it and you'll
 4 answer it. Okay?
 5 A. Okay.
 6 Q. Should the chemists at ZHP have
 7 considered the possibility that the DMF they were
 8 using in the zinc chloride process contained DMA?
 9 Yes or no.
 10 MR. BERNARDO: Object to the
 11 form of the question. Vague. Asked and
 12 answered.
 13 Go ahead.
 14 BY MR. SLATER:
 15 Q. Or you don't have an opinion.
 16 A. Well, as I just mentioned, right?
 17 So this, I need to know if you show a document.
 18 You said a few -- a few days ago this document is
 19 download from this website.
 20 I need to know whether this document
 21 is all the same document is also available when
 22 they actually purchased. You show me two
 23 documents, right? I just want trying to be
 24 scientific here.

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1 Q. You're not being scientific. You're
 2 being evasive.
 3 A. Well --
 4 MR. BERNARDO: Object to the
 5 form of the question. Let's stop with
 6 the characterizations here and arguments.
 7 MR. SLATER: I asked a very
 8 simple question.
 9 THE WITNESS: Can you let me
 10 finish?
 11 MR. SLATER: Maybe you can ask
 12 your witness to answer the question I
 13 asked.
 14 THE WITNESS: Can you please
 15 let me finish?
 16 MR. SLATER: It has nothing to
 17 do with the document.
 18 MR. BERNARDO: Let's --
 19 let's -- let's stop talking over each
 20 other. This is becoming harassing and
 21 I'm, like, let's just take a break and
 22 cool down because this is --
 23 MR. SLATER: No, we're not
 24 taking a break right now. I'm getting --

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1 I have a pending question. I want it
 2 answered.
 3 MR. BERNARDO: Answer the
 4 question and then we're going to take a
 5 break.
 6 BY MR. SLATER:
 7 Q. It's a very simple question, Doctor.
 8 A. Can I speak now?
 9 Q. No, you can't because I'm asking the
 10 question again.
 11 A. Right. So --
 12 Q. Can you answer it with a yes-or-no
 13 answer?
 14 A. I need to first understand the
 15 document and then I will answer the question.
 16 MR. BERNARDO: Dr. Xue, let --
 17 let -- let Mr. Slater ask his question.
 18 Forget about the document. Okay?
 19 BY MR. SLATER:
 20 Q. Should the chemists at ZHP have
 21 considered the possibility that the DMF that they
 22 were using in the zinc chloride process could
 23 contain DMA as an impurity or contaminant of the
 24 DMF? Yes or no, or you have no opinion.

<p style="text-align: right;">Page 154</p> <p>1 A. My opinion is they could, but as I</p> <p>2 said -- can I -- can I speak now?</p> <p>3 Q. I don't know what that means "they</p> <p>4 could."</p> <p>5 Is the answer, yes, they should have</p> <p>6 considered it, no, they shouldn't have, or you</p> <p>7 have no opinion?</p> <p>8 A. They should, but I --</p> <p>9 Q. You answered.</p> <p>10 A. Now, can I speak for myself?</p> <p>11 Q. I'd rather -- look, I can't stop you</p> <p>12 from talking, but you've answered my question.</p> <p>13 A. No.</p> <p>14 Q. No. You told me your opinion.</p> <p>15 A. You said the scope because every of</p> <p>16 my opinion has a scope, right?</p> <p>17 So you showed me one document first.</p> <p>18 On the document there shows this -- this company</p> <p>19 was a supplier for ZHP back to the year 2011 June,</p> <p>20 right?</p> <p>21 And then you showed me a second</p> <p>22 document where you told me you guys download a few</p> <p>23 days ago that shows what the -- the analysis or</p> <p>24 the data of the product of a few days ago, right?</p>	<p style="text-align: right;">Page 156</p> <p>1 the -- the same DMF actually have same kind of</p> <p>2 quality data sheet.</p> <p>3 Q. If the chemists at ZHP knew that DMA</p> <p>4 could be introduced to the zinc chloride process</p> <p>5 as an impurity of the DMF, they needed to take</p> <p>6 that into account when they did a risk assessment</p> <p>7 for the process, correct?</p> <p>8 MR. BERNARDO: Object to the</p> <p>9 form of the question. Calls for</p> <p>10 speculation.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Do you have an opinion, yes or no,</p> <p>13 or you don't have an opinion?</p> <p>14 A. So fact they don't know, right? I</p> <p>15 don't see any direct evidence to show that back</p> <p>16 then at the year 2011 they know. Because what you</p> <p>17 just show me is a website you show me three days</p> <p>18 ago, right? I don't know how many versions of the</p> <p>19 website has been evolved over the past decades. I</p> <p>20 really don't know. I cannot comment.</p> <p>21 And as I said multiple times earlier</p> <p>22 on, too, I'm here as an expert in organic</p> <p>23 chemistry trying to address what the expert from</p> <p>24 the plaintiff side actually raised as their</p>
<p style="text-align: right;">Page 155</p> <p>1 So now you want -- you want to ask</p> <p>2 me question about whether these two document can</p> <p>3 talk to each other. I can't because I have to</p> <p>4 understand and learn what is the specific</p> <p>5 situation you described to me. Okay?</p> <p>6 So, again, the company is supply --</p> <p>7 one of the suppliers back to 2011, and now you</p> <p>8 show me something that is they have a data sheet</p> <p>9 right now have this. I have no reason to</p> <p>10 speculate, but I don't know what their data sheet</p> <p>11 will be like at the year that you talk about</p> <p>12 they -- they serve as a supplier for -- for ZHP.</p> <p>13 So I, as the scientist, I have to be</p> <p>14 very clear about what I'm -- what I'm talking</p> <p>15 about. You talk about one thing over 10 years</p> <p>16 ago. Now you talk about this new discovery three</p> <p>17 days ago and you say -- you try to say this is the</p> <p>18 same thing.</p> <p>19 I can't really comment on that.</p> <p>20 That's why I was pausing. I need to actually</p> <p>21 really understand the situation that you describe.</p> <p>22 If you show me a document back to then or I don't</p> <p>23 even know whether this company would still be the</p> <p>24 best -- the supplier or they -- they actually have</p>	<p style="text-align: right;">Page 157</p> <p>1 comments, right?</p> <p>2 So in there, the four expert in</p> <p>3 their reports, I don't see them talk about</p> <p>4 contamination at all, or I don't remember any of</p> <p>5 the direct evidence to show that there is</p> <p>6 contamination. So I didn't go ahead to address</p> <p>7 that.</p> <p>8 So if there's no evidence to show</p> <p>9 that they have contamination in the report of the</p> <p>10 plaintiffs' expert, I really don't. You ask me</p> <p>11 about opinion back then this and that. Because my</p> <p>12 opinion was -- was trying to address what was</p> <p>13 offered from the plaintiff experts.</p> <p>14 If they have no trouble, they have</p> <p>15 no issue with it, I don't see why I should be here</p> <p>16 to address that.</p> <p>17 And at the end, the only evidence</p> <p>18 I've been aware is this root cause that ZHP did.</p> <p>19 They actually test their DMF, and it showed</p> <p>20 clearly with the data. So I'd like to see what</p> <p>21 exactly data we actually have on our table.</p> <p>22 The data was the DMF they tested</p> <p>23 was -- I think the dimethylamine was like 10 ppm,</p> <p>24 give or take. I might be wrong on the exact</p>

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1 number. And the dimethylamine was probably less
2 than 5 ppm. That's the data, right?

3 So if we have the data and your
4 expert didn't raise any evidence to support that,
5 I just don't know what you expect from me.

6 Q. I expect you to actually just answer
7 my questions and not give me a lecture, honestly.

8 A. I'm sorry. I really don't intend to
9 give anybody lecture.

10 Q. Because with all due respect, this
11 is your first time as an expert, and there may be
12 things that you're not aware of about your role or
13 what would be expected of you.

14 A. I will learn over time.

15 Q. You will, I'm sure. Just like we
16 all do.

17 Did you see any Certificate of
18 Analysis in any document you saw from the
19 suppliers of the DMF to ZHP? Was that in any of
20 the documents you were provided? Did you see
21 that?

22 A. I thought -- you called a lecture.
23 I just I --

24 Q. Just say yes or no or "I don't

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1 know." I mean, why -- why do I need a long
2 speech?

3 Did you see a Certificate of
4 Analysis for the DMF from the manufacturer,
5 supplier, or not? I just want to know if you saw
6 one.

7 MR. BERNARDO: Dr. Xue, if you
8 don't know or you don't recall, just tell
9 Mr. Slater you don't recall having seen
10 them.

11 THE WITNESS: I don't -- I
12 don't recall seeing one.

13 BY MR. SLATER:

14 Q. If you saw the Certificate of
15 Analysis for the DMF and it showed that there was
16 -- that there was DMA in the DMF, that would be
17 important, wouldn't it?

18 MR. BERNARDO: Object to the
19 form of the question. Vague.

20 THE WITNESS: You are
21 speculating, right? So you say if I saw
22 on the certificate that provide me DMF
23 contains -- I don't remember the
24 number -- that amount of DMA, right?

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1 And that definitely is a
2 factor that will take the -- the
3 challenge or that the puzzle to a
4 different level. Because now you know
5 there's this much DMF -- DMA actually
6 present in my solution.

7 BY MR. SLATER:

8 Q. When you did your analysis of what
9 the chemists at ZHP should have done in your
10 report --

11 A. Uh-huh.

12 Q. -- were you evaluating whether or
13 not they should have been aware of potential
14 reactions and potential creation of impurities in
15 their process?

16 A. I like your word "potential" because
17 that's our -- for myself in my career, that's
18 something really we address all the time as well.

19 So as a scientist, we -- we do
20 that all the time, right? So potential side
21 reactions is definitely something we talk on daily
22 basis. Every project almost every reaction,
23 unfortunately, you always have something.

24 So as a chemist, as you asking,

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1 right? So, yes, I think that's very important to
2 actually understand or trying to figure out,
3 foresee things.

4 But everything, unfortunately, has a
5 scope, right? So you have a project. You have
6 your idea. You have your thought based on what
7 you learn was made available to you. You can't --
8 you can't actually try to foresee or predict
9 what -- what potential things out there I'm trying
10 to duck or get away from.

11 But that's -- that's the reality,
12 right? So what's -- what's available big, bit
13 question, right? So you need to -- you need to
14 really try your best to optimize the scope that
15 you can be foresee things. But, unfortunately, as
16 scientists, we never do. We never do, especially
17 for chemistry, right?

18 So people say chemistry is
19 experiment. Unless you have the experiment to
20 show, okay, this condition that will happen,
21 right? So it's hard. Although you can learn
22 through textbook, through -- through your advisor
23 and things, but there's really just those
24 potentials you cannot always predicting.

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1 So you try the hardest try to -- to
2 actually help yourself, but, unfortunately, that's
3 not means you can -- you can foresee everything
4 out there.
5 Q. Are you aware of whether or not ZHP
6 was required to ensure that there were no
7 genotoxic impurities in the valsartan it was
8 manufacturing?
9 MR. BERNARDO: Object to the
10 form of the question.
11 THE WITNESS: Well, as I
12 said --
13 MR. BERNARDO: Wait. Dr. Xue,
14 hold on. Let me get my objection.
15 Object to the form of the
16 question. Beyond the scope of his expert
17 opinion. Compound.
18 Go on. You can answer,
19 Dr. Xue.
20 THE WITNESS: Well, the
21 Internet was not very stable.
22 But I'm not a regulatory
23 scientist. About these requirement or
24 regulatory science-related questions, I

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1 really not sure whether I'm the right
2 person to ask.
3 MR. BERNARDO: And, Adam, I'll
4 repeat. When we're at a breaking point.
5 We've been going an hour and a half.
6 MR. SLATER: We can do it
7 right now.
8 MR. BERNARDO: Okay. Great.
9 THE VIDEOGRAPHER: Going right
10 now.
11 MR. BERNARDO: I think the
12 logical time for a lunch break.
13 MR. SLATER: Fine. How long
14 do you want?
15 MR. BERNARDO: Dr. Xue, how
16 long --
17 THE VIDEOGRAPHER: The time is
18 12:54 p.m. We're off the record.
19 (Whereupon, at 12:54 p.m., a
20 luncheon recess was taken.)
21
22
23
24

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1 AFTERNOON SESSION
2 (1:33 p.m.)
3 FENGtian XUE, PHD
4 called for continued examination and, having been
5 previously duly sworn, was examined and testified
6 further as follows:
7 EXAMINATION (CONTINUED).
8 THE VIDEOGRAPHER: Time right
9 now is 1:33 p.m. We're back on the
10 record.
11 MR. SLATER: Okay. Let's put
12 up as Exhibit -- is it 8 that we're up
13 to?
14 We're going to put up an
15 article as Exhibit 8. Let's get it up
16 there.
17 (Document marked for
18 identification as Xue Exhibit 8.)
19 BY MR. SLATER:
20 Q. Now, Exhibit 8 is an article titled
21 "Dimethylformamide: Purification Tests For Purity
22 and Physical Properties" dated in 1977.
23 Do you see this?
24 A. Yes, I can see by your reading.

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1 That's correct.
2 Q. And we saw this on your supplemental
3 list of materials reviewed.
4 Do you recall reading this?
5 A. I -- I think so.
6 Q. And this is published by the
7 International Union of Pure and Applied Chemistry
8 in 1977.
9 Do you see that?
10 A. That is correct. 1977.
11 Q. Let's go -- obviously we don't have
12 -- let's go to page 887, please, and we'll go to
13 the top half of the page.
14 MR. SLATER: Can you blow that
15 up, please, Chris?
16 BY MR. SLATER:
17 Q. And if you go down almost halfway
18 down the page, after the first formula, there's a
19 sentence that starts with the word "Formic acid."
20 Do you see that?
21 A. Yes, I do see formic acid.
22 Q. It says:
23 "Formic acid and dimethylamine are
24 thus predominant impurities in DMF and determine

<p style="text-align: right;">Page 166</p> <p>1 the odor of the impure solvent."</p> <p>2 Do you see that?</p> <p>3 A. Yes, by reading. That's correct.</p> <p>4 Q. You would agree with me that the</p> <p>5 fact that DMF may contain DMA as an impurity was</p> <p>6 something that a chemist who was working with DMF</p> <p>7 in a manufacturing process for a drug product</p> <p>8 should have known, correct?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question.</p> <p>11 THE WITNESS: I disagree.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. Let me ask you this question.</p> <p>14 Let's talk about what ZHP did with</p> <p>15 its processes, the TEA with sodium nitrite</p> <p>16 quenching and zinc chloride process.</p> <p>17 You're familiar with both processes,</p> <p>18 right?</p> <p>19 A. Yes.</p> <p>20 Q. And you're familiar with the fact</p> <p>21 that it was ZHP that developed those processes,</p> <p>22 correct?</p> <p>23 A. The process of TEA with quenching</p> <p>24 and zinc chloride was -- for manufacture was</p>	<p style="text-align: right;">Page 168</p> <p>1 develop their own.</p> <p>2 Q. Did the TEA process with sodium</p> <p>3 nitrite quenching -- was that something that was</p> <p>4 in use before ZHP started using it? That</p> <p>5 integrated process, did that exist before ZHP used</p> <p>6 it?</p> <p>7 A. Maybe I didn't make myself clear.</p> <p>8 So the chemistry part are known, but</p> <p>9 both ZHP -- TEA with quenching process or the zinc</p> <p>10 chloride process. But for in term of API</p> <p>11 synthesis using those chemistry, I think ZHP, they</p> <p>12 actually patent those.</p> <p>13 Q. When ZHP created those processes,</p> <p>14 they knew that they were going to introduce</p> <p>15 chemicals and solvents and various substances into</p> <p>16 the process, right?</p> <p>17 A. Yes. When they actually develop</p> <p>18 these process, they knew they're going to use</p> <p>19 reagents and solvent and patent everything in the</p> <p>20 process.</p> <p>21 Q. And do you agree that responsible</p> <p>22 chemists under those circumstances would need to</p> <p>23 understand the potential risks of introducing</p> <p>24 those various chemicals and substances and</p>
<p style="text-align: right;">Page 167</p> <p>1 developed by ZHP, but the chemistry part was not</p> <p>2 developed by ZHP because there are -- these</p> <p>3 reactions have been out there before they actually</p> <p>4 used in their projects.</p> <p>5 Q. The manufacturing processes that</p> <p>6 were titled the TEA with -- jeez. Let me start</p> <p>7 over.</p> <p>8 What -- what do you mean by what you</p> <p>9 just said when you -- when you provided that --</p> <p>10 A. Well, like in --</p> <p>11 Q. -- explanation at the end? I don't</p> <p>12 understand.</p> <p>13 A. -- my lab -- my lab develop a</p> <p>14 reaction, I publish this reaction or I patent this</p> <p>15 reaction. And then you if you own a lab, you can</p> <p>16 actually use my reaction published to develop your</p> <p>17 own process. You can use mine.</p> <p>18 So ZHP for their TEA process or the</p> <p>19 zinc chloride process, all these particular</p> <p>20 reactions in their process was not invented by</p> <p>21 them or developed by them. They are there before</p> <p>22 these two processes are -- are established.</p> <p>23 They use other people's work and</p> <p>24 develop their own. They use other people's to</p>	<p style="text-align: right;">Page 169</p> <p>1 reactions? Do you agree that they needed to</p> <p>2 understand the risks of doing that?</p> <p>3 MR. BERNARDO: Object to the</p> <p>4 form of the question. Vague.</p> <p>5 THE WITNESS: Right. For</p> <p>6 these particular processes, right, when</p> <p>7 you have API of valsartan in your mind,</p> <p>8 you have these organic we call it</p> <p>9 reaction of scheme.</p> <p>10 So those are designed and then</p> <p>11 they should actually know. Everybody</p> <p>12 when they actually develop something,</p> <p>13 they will based on their knowledge need</p> <p>14 to know what are the risks, and then they</p> <p>15 will try to avoid those risks.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. And they had to take into account</p> <p>18 that what they were manufacturing was going to be</p> <p>19 placed into a medication that people were going to</p> <p>20 take and put in their bodies, right?</p> <p>21 That was the purpose of what they</p> <p>22 were manufacturing was to create drugs to put in</p> <p>23 people's bodies, right?</p> <p>24 A. Manufacturer, yes. The ultimate</p>

<p style="text-align: right;">Page 170</p> <p>1 goal is definitely to -- to make drugs and people 2 can take. 3 I don't -- because what was the 4 question? So what's their responsibility about 5 what were you asking? 6 Q. It was a simple question. 7 When the -- when they were -- 8 rephrase. 9 The chemists who were involved in -- 10 A. Uh-huh. 11 Q. -- these processes had to understand 12 that what they were manufacturing was intended to 13 be placed into pills that were going to go into 14 the human body, correct? 15 A. Yeah. So the -- the manufacturing 16 chemist, as you mention, right, they -- they -- 17 they should be very clear of the ultimate goal of 18 their work will be eventually become pills for 19 patients. 20 Q. And you would agree that with regard 21 to the various substances -- well, rephrase. 22 When ZHP changed -- well, rephrase. 23 You understand that ZHP had four 24 different processes to manufacture valsartan over</p>	<p style="text-align: right;">Page 172</p> <p>1 no reason to form nitrosamines. 2 Q. When they developed the TEA with 3 sodium nitrite quenching process, that process has 4 the potential to create nitrosamines, correct? 5 A. As you asked for now, it's a fact. 6 This process did already produce nitrosamine. 7 Q. If -- 8 A. So everybody knows now. Sorry. 9 Q. If there was no sodium nitrite or 10 other pathway to create -- to injecting a 11 nitrosating agent into the process, there would be 12 no risk of creating a nitrosamine, correct? 13 A. Well, nitrosamine is formed from two 14 parts, right? You have, like you said, a 15 nitrosating agent in different forms that, and 16 then you also have to have a secondary amine 17 there. So these two must be there to form 18 nitrosamine. So if you remove one of the two, 19 then nitrosamine will not formed, at least based 20 on my knowledge. 21 Q. And with regard to the zinc chloride 22 process, the same would hold true. Without the 23 sodium nitrite that was part of the process, there 24 would be no potential to create a nitrosamine,</p>
<p style="text-align: right;">Page 171</p> <p>1 the course of time. You're aware of that, right? 2 The Tin Process, the TEA process, 3 the sodium nitrite quenching process, and the zinc 4 chloride process, right? 5 A. That's -- that's correct. 6 Q. The original process, the Tin 7 Process, you looked at the chemistry of that 8 process, right? 9 A. Yes, I did look into the chemistry 10 of the Tin Process. 11 Q. And based on your review, there were 12 no reactions that are in that process capable of 13 creating a nitrosamine, correct? 14 A. Right. If you ask me now when I -- 15 when I look at this based on my -- my knowledge 16 now, there's no chance for nitrosamine formation 17 based on my knowledge now. I mean, in the future 18 if we discover, that's -- that's -- that's a 19 different story. But now, no. 20 Q. And the same would hold true for the 21 TEA process, the first TEA process, before they 22 had sodium nitrite quenching, correct? 23 A. Yeah, with the scope of the 24 knowledge that I have, there's no -- no -- there's</p>	<p style="text-align: right;">Page 173</p> <p>1 correct? 2 A. Similar to what I said. You need 3 two parts to form a nitrosamine. If -- if you 4 don't, if you cut two -- one of the two parts, 5 either one of the two, then you will not have a 6 chance, based on what I learned. 7 Q. In terms of understanding potential 8 risks, when ZHP chose to introduce sodium nitrite 9 into the quenching process, they needed to 10 understand that if that was exposed to a secondary 11 amine, that could create a nitrosamine, correct? 12 The chemists at least need to have 13 that understanding at the basic level who were 14 creating this process, right? 15 A. I disagree. I think -- 16 Q. So you disagree. That's fine. I 17 just asked if you agree or disagree. I didn't ask 18 you why. 19 A. Okay. 20 Q. Were the chemists who decided to 21 introduce sodium nitrite into the sodium 22 nitrite -- rephrase. 23 The chemists who determined to 24 introduce sodium nitrite quenching into the TEA</p>

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1 process, as well as into the zinc chloride
2 process, were they responsible to understand the
3 risks of using sodium nitrite in that process?
4 MR. BERNARDO: Object to the
5 form of the question. Vague.
6 THE WITNESS: You are asking
7 me if the chemists who introduce sodium
8 nitrite into the quenching process of
9 either the zinc chloride or the TEA with
10 quenching process will be responsible for
11 the formation of nitrosamine. That was
12 your question?
13 BY MR. SLATER:
14 Q. No. My question is: When ZHP --
15 well, rephrase.
16 When the chemists decided to
17 introduce sodium nitrite to quench the sodium
18 azide, they needed to evaluate the risks of using
19 sodium nitrite in that process.
20 You would agree that was something
21 they had to assess and evaluate, right?
22 MR. BERNARDO: Object to the
23 form of the question. Vague.
24 THE WITNESS: So when they

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1 actually introduce any reagent to a
2 process to any of the reactions, they
3 need to know what they add, right? And
4 also they need to track it down to know
5 where this component ends.
6 So that -- if that's the
7 question, the question is yes. So you
8 should be able to or you should actually
9 track it down and know where the chemical
10 add, where it is.
11 BY MR. SLATER:
12 Q. And they need to research to
13 understand the potential risks of using sodium
14 nitrite in that process. They needed to
15 understand what are the potential risks of
16 introducing this to the process.
17 That's the responsible thing to do,
18 right?
19 MR. BERNARDO: Object to the
20 form of the question. Vague. Compound.
21 THE WITNESS: Well, when --
22 when we introduce any reagent like sodium
23 nitrite, so you need to know what you
24 want to use this for, right? So that

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1 want to use as you introduce as a
2 quenching reagent, you want to quench the
3 excess of amount of azide.
4 And then they want to also
5 have a way to track it down to see where
6 it ends, right, so you will know where
7 whether this sodium nitrite they actually
8 introduce will be enough in the final
9 product of things.
10 So that's I think something a
11 chemist who actually develop this process
12 should know.
13 In term of whether they would
14 be aware this sodium nitrite can become a
15 nitrosating reagent, I disagree. I think
16 that's something you're not easily aware.
17 BY MR. SLATER:
18 Q. Do you have any understanding of the
19 level of scientific analysis that the people
20 working at ZHP were required to conduct based on
21 the regulations and the standard operating
22 procedures that applied to them?
23 MR. BERNARDO: Again, object.
24 Dr. Xue is not being offered as a

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1 regulatory expert.
2 If you can answer it, go
3 ahead.
4 THE WITNESS: Yeah, it's out
5 of my expertise. I cannot comment on
6 that.
7 BY MR. SLATER:
8 Q. So you don't have an opinion as to
9 the extent of scientific research that was
10 expected of the chemists at ZHP in connection with
11 the development and use of the zinc chloride and
12 sodium nitrite quenching TEA processes?
13 MR. BERNARDO: Object to the
14 form of the question. Mischaracterizes
15 his prior testimony.
16 THE WITNESS: I do have
17 opinion on that.
18 BY MR. SLATER:
19 Q. Okay. So you do have an opinion as
20 to what extent of scientific research was required
21 of the chemists at ZHP --
22 A. Well --
23 Q. -- by as a matter of the regulations
24 and FDA guidances and internal SOPs that applied

<p style="text-align: right;">Page 178</p> <p>1 to them?</p> <p>2 Do you have an understanding of that</p> <p>3 and an opinion as an expert?</p> <p>4 MR. BERNARDO: Object to the</p> <p>5 form of the question and the</p> <p>6 characterization of his prior testimony.</p> <p>7 THE WITNESS: I can't comment</p> <p>8 on regulatory science, but I said I have</p> <p>9 opinion on ZHP had within their scope of</p> <p>10 knowledge their -- their task a risk</p> <p>11 assessment in term of chemistry to</p> <p>12 actually before they actually make any</p> <p>13 change.</p> <p>14 Because as you said, there --</p> <p>15 there are four different processes they</p> <p>16 do. So each one of the change, they have</p> <p>17 done multistep analysis for their</p> <p>18 reactions each one of them to do those</p> <p>19 analysis.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. Were the chemists at ZHP obligated</p> <p>22 to determine whether the changes to the</p> <p>23 manufacturing processes could introduce genotoxic</p> <p>24 impurities to those processes?</p>	<p style="text-align: right;">Page 180</p> <p>1 DNA modifiers actually are the biggest</p> <p>2 drug on the market. They treat cancer,</p> <p>3 right? So those are by some sort of</p> <p>4 definition can be quantified -- qualified</p> <p>5 as genotoxic. But they are actually out</p> <p>6 there for -- for patient treatment,</p> <p>7 right?</p> <p>8 So disease or even -- even the</p> <p>9 dosage format matters, too. Because some</p> <p>10 drug at a low dose, they can be helpful</p> <p>11 for -- for disease.</p> <p>12 So like, for instance, if you</p> <p>13 treat people with, you know, with</p> <p>14 infections antibiotics, some of the</p> <p>15 nitrous oxide-released molecules can</p> <p>16 be -- can be drugs, but when you have a</p> <p>17 high dose, they are actually can be</p> <p>18 toxic. They cause cancer sometimes.</p> <p>19 So it really depends on who</p> <p>20 you actually talk about, what the patient</p> <p>21 you talk about, what disease you talk</p> <p>22 about, what dose level you talk about.</p> <p>23 Yeah. So, again, I'm not a</p> <p>24 regulatory science scientist. I cannot</p>
<p style="text-align: right;">Page 179</p> <p>1 MR. BERNARDO: Object to the</p> <p>2 form of the question. Vague.</p> <p>3 THE WITNESS: So genotoxic</p> <p>4 impurities itself is a pretty broad</p> <p>5 concept. So can you be more specific</p> <p>6 like what we talk about here?</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Do you have any understanding as to</p> <p>9 whether or not, or to what extent, ZHP was</p> <p>10 required to evaluate these manufacturing processes</p> <p>11 for the potential creation of genotoxic</p> <p>12 impurities?</p> <p>13 MR. BERNARDO: Object to the</p> <p>14 form of the question. Vague.</p> <p>15 THE WITNESS: Well, although</p> <p>16 I'm not -- as I said, I'm not a</p> <p>17 regulatory science expert, but I know</p> <p>18 that genotoxic species is very broad</p> <p>19 topic. It's actually, you know, these</p> <p>20 toxic definition is also very vague. It</p> <p>21 depends on what disease you talk about.</p> <p>22 Like some of the disease, you</p> <p>23 know, toxic molecule may not be too bad.</p> <p>24 Like I do cancer research. Some of the</p>	<p style="text-align: right;">Page 181</p> <p>1 really tell you what are the required --</p> <p>2 requirements are for -- for ZHP chemist</p> <p>3 to actually know about.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. In the context of the processes to</p> <p>6 manufacture valsartan -- which is not a cancer</p> <p>7 drug, right?</p> <p>8 A. It's -- it's for high blood</p> <p>9 pressures.</p> <p>10 Q. In the context of the processes that</p> <p>11 we're talking about, the TEA with sodium nitrite</p> <p>12 quenching and the zinc chloride process --</p> <p>13 A. Right.</p> <p>14 Q. -- what level of scientific analysis</p> <p>15 was required of ZHP in order to investigate the</p> <p>16 potential for the creation of genotoxic impurities</p> <p>17 in those processes?</p> <p>18 Do you have any understanding of</p> <p>19 what level of scientific research was required?</p> <p>20 MR. BERNARDO: Object to the</p> <p>21 form of the question.</p> <p>22 THE WITNESS: For the level</p> <p>23 of requirement for scientific research, I</p> <p>24 didn't read much, but I read the -- the</p>

<p style="text-align: right;">Page 182</p> <p>1 FDA's announcement about these particular 2 potential genotoxic compound. They were 3 saying either NDMA from the zinc chloride 4 process or the NDEA from the TEA with 5 quenching process, they are just 6 possible, probable cancer-causing 7 reagent. 8 I remember FDA also highlight 9 in their announcement that even for the 10 patient with the highest dose of these 11 drugs, valsartan I think is over 300 12 milligram per -- per day for 4 years of 13 full treatment. Like they were saying, 14 if you have 8,000 something like that 15 patient, you possibly can have one 16 additional patient with cancer. So 17 that's -- that's how small the chance 18 will be. 19 So, again, I'm not a 20 regulatory science scientist, but I just 21 feel this is not -- well, that's the fact 22 that I read from -- from the FDA website. 23 BY MR. SLATER: 24 Q. Thank you but not what I asked you.</p>	<p style="text-align: right;">Page 184</p> <p>1 "Owing to its various modes of 2 degradation (hydrolysis, thermal and photochemical 3 decomposition) the principal impurities found in 4 DMF are: dimethylamine" and then it lists some 5 others. 6 Do you see that? 7 A. I do see that. 8 Q. First of all, you agree with me that 9 degradation of dimethylformamide can be caused 10 by -- by thermal cause, right? That's by 11 temperature, correct? 12 A. By reading that, that's what they 13 talk about. 14 Q. Well, you agree that's accurate, 15 right? 16 A. Where now we all learn that that 17 could actually happen. 18 Q. Well, this is -- this was published 19 in 1977. 20 So people knew in 1977 that DMF 21 could be degraded by temperature, right? 22 A. By reading that, that -- that is 23 what the author said. 24 Q. It was also known that DMF could be</p>
<p style="text-align: right;">Page 183</p> <p>1 Do you have an opinion as to the 2 level or extent of scientific research that ZHP 3 was required to conduct when it was developing 4 these processes in order to determine whether 5 there was a potential for the creation of 6 genotoxic impurities through these new processes 7 that they created? Yes or no. 8 A. I don't know the requirement because 9 I'm really not a regulatory scientist. I don't 10 know what the requirement ZHP had -- ZHP has to 11 follow to perform their research. 12 Q. Let's go within that document to 13 page 890, Exhibit 8. The article on 14 dimethylformamide from the International Union of 15 Pure and Applied Chemistry. Very top it says 16 "Tests For Purity." 17 Do you see that? 18 A. Yes. 19 Can you make it bigger, please? 20 Thank you. 21 Q. It's too big. 22 A. No, that's okay. Thank you. 23 Q. Okay. At the top of page 890, it 24 says "Tests For Purity."</p>	<p style="text-align: right;">Page 185</p> <p>1 degraded by hydrolysis, correct? 2 A. Yes, by reading, that's also there, 3 too. 4 Q. That's also a true statement in 5 chemistry, right? That DMF can be degraded by 6 hydrolysis, right? 7 A. That's the authors -- what the 8 authors wrote there. That's correct. 9 Q. Do you disagree? 10 A. Well, as a chemist, I always have to 11 be very specific with the conditions, right? So 12 like hydrolysis is -- it's a type of reactions, 13 right? Thermal or photochemical decomposition 14 also covers a whole spectrum of conditions. 15 So I -- you know, by saying this it 16 just say you're eventually you're going to die, 17 right? So that -- that is too vague as a 18 condition that is given. Because I'm not against 19 this. What I'm saying is by saying what I'm 20 saying here is really, it doesn't tell me what 21 condition the author is trying to actually 22 describe. 23 Q. What does hydrolysis mean? 24 A. Hydrolysis means when you have a</p>

<p style="text-align: right;">Page 186</p> <p>1 substance in the presence of water, the water can 2 actually attack the substance so that you can 3 actually form a product from water attacking. 4 Q. Okay. And you'll agree with me that 5 under certain circumstances -- I don't want to go 6 through a whole dissertation on it -- but under 7 certain circumstances, it's known and was known as 8 of at least 1977 that DMF could be degraded by 9 hydrolysis, correct? 10 A. Well, that's what the author said. 11 As -- as I just explained to you, hydrolysis is a 12 very broad type of reaction condition. They can 13 be actually happening in acidic or basic or 14 neutral conditions, or having other additives add 15 in there, too. Hydrolysis normally coupled with a 16 specific temperature as well as their 17 concentration. 18 So, yeah. So this is just describe 19 a very general broad type of reaction. That 20 doesn't tell me what specific condition, you know, 21 it will be used. 22 So, in other words, by just reading 23 this, I saw, okay, there's these authors claim 24 that potentials. But I won't know, for instance,</p>	<p style="text-align: right;">Page 188</p> <p>1 that you -- you will have a goal. You have 2 established a hypothesis that you reach out to see 3 something that is happening. 4 But I always say, if I don't know 5 what could happen, and then I would not probably 6 not establish an experiment and try to prove 7 something that I didn't expect. 8 So I hope I explain this like clear. 9 So you have to first have a goal, and then you 10 design something to achieve the goal. 11 Q. When it was decided by ZHP to use 12 DMF, if they had done research -- which we know 13 they didn't -- into the possible degradation or 14 impurities of DMF, they would have been able to 15 find literature like what I'm showing you right 16 now to know that under certain circumstances DMF 17 could introduce DMA into a process. 18 They would have at least known that 19 as a general point if they had done the research, 20 right? 21 A. If they done the research, they read 22 this paper. If I'm the person at ZHP, I do this. 23 I look at this. I say, oh, under hydrolysis, 24 which means in the presence of water. So that's a</p>
<p style="text-align: right;">Page 187</p> <p>1 what temperature will cause this or what kind of 2 concentration will cause this or how much acid or 3 base it will require to cause this. 4 Q. The best way to know if a certain 5 manufacturing process will cause degradation of 6 DMF would be to run a test, right? Run a test 7 under the circumstances under which the process is 8 going to be run and see what happens. 9 If you really want to know if that 10 process can cause that reaction, you can do a 11 test, right? That's -- that's something that you 12 can do, right? 13 A. Well -- 14 Q. Yes or no. Can you run a test? 15 A. You can run a test, but that's under 16 assumption that you know what could happen. 17 So it's like all research I do is we 18 call it hypothesis-driven, right? So you have a 19 idea. You thought something could happen. Then 20 you go out to establish a chemistry or a reaction 21 or a procedure trying to test that. But that's 22 how you make your steps. You move your chemistry 23 or you make your science forward. 24 So, you know, it's very, very common</p>	<p style="text-align: right;">Page 189</p> <p>1 very general situation. Or you have a thermal or 2 a photo. None of these are actually giving me any 3 direct evidence about what is really required. 4 This is basically telling me all the 5 environment, right? 6 Q. Right. 7 A. So we have moistures are run. We 8 have, you know, you have some sort of temperature 9 run. You always have light in the lab unless you 10 have a dark room. 11 So these are to me, yes, they are 12 statement, right? They are -- they are published. 13 They are available. ZHP, they do analysis. They 14 definitely have a chance to read this paper. They 15 can actually come to this paragraph to -- to read 16 this statement in particular. 17 But I put myself at that -- their 18 situation. If I read this, it won't actually help 19 me to understand a lot. 20 Excuse me. Sorry. 21 Q. It's okay. 22 If ZHP wanted to do a thorough risk 23 assessment for the introduction of DMF and to know 24 whether or not DMA would be created or be</p>

<p style="text-align: right;">Page 190</p> <p>1 introduced into the process, there were certain 2 tests they could have done, and I showed you in 3 the deviation investigation report they did tests. 4 Those could have all been done in 5 the beginning if they had chosen to do them, 6 correct? 7 MR. BERNARDO: Object to the 8 form of the question. Compound. Vague. 9 THE WITNESS: The situation 10 is, if they know. Like we are discussing 11 now. Yes, they -- they actually have a 12 method as you've shown, right? If they, 13 you know, they can do the test. 14 But the problem for -- for us 15 is back to 2012 or '13 when they are 16 trying to develop these new processes 17 back then. They don't know that and, you 18 know, the very little information around 19 there -- not saying there's nothing, 20 right? So you shown me multiple 21 documents already. 22 They are not -- to my opinion, 23 they are not give ZHP the hint that they 24 are potentially have trouble of</p>	<p style="text-align: right;">Page 192</p> <p>1 Which one is it: The general 2 chemist walking down the street or the chemist 3 who's actually developing a drug manufacturing 4 process and making choices as to what chemicals to 5 introduce to that process? 6 I just want to know. Is it A or B? 7 A. I cannot speak for that, really. 8 I'm a chemist. I view myself as the expert in 9 organic chemistry, but just now when I speak, I 10 really view I myself as an average chemist. 11 I myself will not be aware of that. 12 So I don't say I'm much better than the people at 13 ZHP. They need to actually develop a process for 14 drug purpose. I fully respect that. They are -- 15 they are smart. They are high-level chemists. 16 Excuse me. 17 But the same time I say myself, if I 18 put myself at that -- their shoes, I won't be able 19 to. 20 Q. Did you read in evaluating -- 21 rephrase. 22 When you went through the factual 23 information to form your opinions -- 24 A. Uh-huh.</p>
<p style="text-align: right;">Page 191</p> <p>1 generating dimethylamine. I was just not 2 seeing that myself. 3 BY MR. SLATER: 4 Q. Well, I've shown you literature and 5 I could keep showing it to you indicating, 6 number one, that it was known that DMA was a known 7 impurity of commercially sold DMF. 8 That was something that ZHP could 9 have easily known, right? 10 A. I disagree. 11 Q. Okay. You disagree. Okay. 12 A. This -- even this moment I don't 13 think, right? So average chemist can -- can 14 easily know -- 15 Q. Yeah. 16 A. -- that there -- there in their -- 17 in their DMF they have DMA. 18 Q. Is the standard you're applying for 19 your opinions what the average chemist in the 20 world would know, or is the standard what a 21 process chemist working at a drug manufacturer 22 who's creating a process to manufacture a drug 23 that's going to go into the human body, which is a 24 regulated area, is that the standard?</p>	<p style="text-align: right;">Page 193</p> <p>1 Q. -- did you see anywhere where ZHP 2 said that the DMA could have been introduced both 3 through degradation of the DMF or as an impurity 4 of the DMF? Did you see whether -- what ZHP said 5 on that topic? 6 MR. BERNARDO: Object to the 7 form of the question. Vague. 8 THE WITNESS: As far as I 9 remember, when I reviewed the material to 10 form my opinion, I didn't see ZHP talk 11 about introduction of DMA. Because they 12 just don't even know that. 13 But as you show me this 14 morning, when they do this call deviation 15 study or the -- the root cause study when 16 they know in their process, 17 unfortunately, this particular compound 18 was formed, they did go back to actually 19 try to figure out what was the cause of 20 how it's actually formed. 21 BY MR. SLATER: 22 Q. And when you looked at that 23 analysis, did you see that ZHP concluded that the 24 DMA could have been introduced both as an impurity</p>

<p style="text-align: right;">Page 194</p> <p>1 of the DMF and/or as a degradation product of the 2 DMF during the process? 3 Did you see that in the deviation 4 investigation report? Did you -- I just want to 5 know if you saw that. 6 A. Off my head, I honestly I cannot say 7 for sure I saw that, but that's what I remember, I 8 can tell you. But if you can put up a document to 9 show me, I'll confirm that. But my -- my -- 10 Q. Sure. Let's go to the deviation 11 investigation report, page 7. Same exhibit, 12 Number 5. 13 A. Thank you. 14 Q. That's the report I'm using. Page 7 15 of 236. Very bottom of the page. 16 A. So you said the very bottom of the 17 page 11 -- 18 Q. Page 7 of 236. 19 A. I'm sorry. 20 Q. The bottom of the page. 21 A. 7. 22 Q. And you see it says that: 23 "Based on the investigation and 24 evaluation of the current Valsartan route of</p>	<p style="text-align: right;">Page 196</p> <p>1 just -- they just threw out some hypothesis there. 2 Q. Okay. It then says: 3 "Furthermore, during the tetrazole 4 formation step, dimethylformamide may be 5 susceptible to low level decomposition under high 6 temperature to produce trace amount of 7 dimethylamine either via thermo decomposition or 8 hydrolysis." 9 Do you see that? 10 A. I saw that, too. 11 Q. And do you agree with me that the 12 DMF that was introduced to the zinc chloride 13 process may have contained trace amounts of 14 dimethylamine as an impurity at the time that it 15 was being used for the manufacturing? Do you 16 agree with that? 17 A. You said may contain that, right? 18 Q. Yes. Do you agree with that? 19 A. Yes, it is possible. 20 Q. And do you also agree that during 21 the tetrazole formation step, the DMF may have 22 decomposed under the temperatures that were 23 applied to it to produce trace amounts of 24 dimethylamine either via thermal decomposition or</p>
<p style="text-align: right;">Page 195</p> <p>1 synthesis (zinc chloride process), this 2 impurity -- which they're referring to NDMA -- is 3 most likely formed during the 'azide quenching' by 4 nitrous acid of the API manufacturing process." 5 Do you see that? 6 A. Yes, I do see that. 7 Q. "Specifically, DMF, one of the 8 solvents used in Step 4 (Crude) stage, may contain 9 trace amount of dimethylamine as an impurity." 10 Do you see that? 11 A. I saw that, too. 12 Q. Do you know when ZHP first learned 13 that DMF can contain dimethylamine as an impurity? 14 A. I don't know when they first learned 15 that, but based on what you read just now, I'm 16 reading this paragraph, too. They are saying -- 17 Q. I just asked if you know when they 18 learned that. It's the only question I asked you. 19 A. I don't know when they learned that 20 specifically. 21 But I just want to point out they 22 say "may contain trace amounts." So they are 23 actually -- I don't think this paragraph is 24 showing they know for sure what happened. They</p>	<p style="text-align: right;">Page 197</p> <p>1 hydrolysis? 2 Do you agree that's a true 3 statement, also? 4 A. Again, they are -- they are 5 hypothesizing here, right? They are trying to -- 6 Q. Do you agree with the statement or 7 not? 8 A. I agree with what they said. That's 9 the two possibilities what can actually cause the 10 formation of dimethylamine. 11 I don't see any direct evidence to 12 show to support these are the case, though, or 13 either one or both are the case. Or maybe not 14 these two, but a third one. So because they point 15 out these are two may -- maybe, right? So that 16 means there are possibly other ones as well. 17 Q. If you look at the bottom of 18 page 8 -- go to the bottom of page 8 -- it says: 19 "Based on the above elucidated root 20 cause, the presence of trace amount of NDMA in the 21 final Valsartan API requires the convergence of 22 the following three factors (hence the 'Three 23 Factors Analysis')." 24 Did you see what I just read?</p>

<p style="text-align: right;">Page 198</p> <p>1 A. Yes, as you read, that's the last 2 paragraph on page 8. 3 Q. Right. 4 Before right now, were you aware of 5 the Three Factors Analysis that was applied by ZHP 6 in its root cause investigation? 7 A. Yes. 8 Q. Did you talk about the Three Factors 9 Analysis in your report? 10 I don't remember seeing it. Did 11 you? 12 It's just a yes-or-no question, 13 Doctor? 14 A. I didn't mention that in my e-mail 15 -- in my report because again -- 16 Q. That's all I asked. I didn't ask 17 you why. I just asked if it's there or not. 18 A. No, it's not there. 19 Q. Let's go to the top of page 9 where 20 the three factors are listed. 21 Number 1. "Presence of 22 dimethylamine in the manufacturing process, such 23 as its presence in tetrazole formation step." 24 Do you see that?</p>	<p style="text-align: right;">Page 200</p> <p>1 day one because they knew that they were going to 2 put in sodium nitrite and hydrochloric acid and 3 that was going to form nitrous acid, right? 4 A. Yes, I believe so. 5 Q. Number 3. "The possibility of 6 direct contact between secondary amines and 7 nitrite in the presence of the target product." 8 That's number 3, right? 9 A. That's by reading, that's number 3. 10 Q. And in the zinc chloride process, we 11 know the NDMA formed when the dimethylamine was 12 contacted by the nitrous acid, right? 13 A. Well, technically, it's not nitric 14 acid. It's the nitrosonium ion that's formed 15 through multiple steps from nitric acid. 16 Q. The presence of the nitrous acid was 17 necessary to form the NDMA, correct? 18 A. For -- for this particular reaction 19 talk about here, it is correct. 20 But I want to say that nitric acid 21 is not the only reagent that can actually generate 22 nitrosative agent. 23 Q. There's many potential nitrosative 24 agents in the world, but the one that was in this</p>
<p style="text-align: right;">Page 199</p> <p>1 A. I see that sentence. 2 Q. And you agree that the key is that 3 the diethylamine is present. It doesn't matter 4 how it gets there, whether it was an impurity of 5 the DMF to begin with or whether it was a 6 degradation product from the process. 7 It doesn't matter how it gets there. 8 It just matters that it can be there, right? 9 A. For the formation of the NDMA, 10 dimethylamine, as far as we now know as 11 scientists, it's required for the reaction since 12 we know dimethyl -- NDMA is formed during this 13 process. So it's going to be somewhere on the 14 process they have it. 15 Q. It doesn't matter how it got there. 16 It just matters that it was there, right? 17 A. Yes. 18 Q. Number 2. "Presence of nitrous acid 19 in the manufacturing process, such as quenching of 20 azide using sodium nitrite." 21 That's number 2, right? 22 A. That is number 2 by reading. 23 Q. The presence of nitrous acid in this 24 process was well known to the people at ZHP from</p>	<p style="text-align: right;">Page 201</p> <p>1 process was nitrous acid, right? 2 A. No, it's nitrosonium ion. It's not 3 a reagent that's directly from nitric acid. You 4 have -- we have to be clear about that. Because 5 nitric acid is not a nitrosative reagent. It's 6 nitrosonium ion. 7 Q. The nitrosonium ion, you call that 8 as NO plus in your report, right? 9 A. I draw it that way, yes. 10 Q. Could there have been NO+ without 11 the sodium nitrite? 12 A. For this particular reaction, no. 13 Q. So the introduction of the sodium 14 nitrite led to the creation of nitrous acid, and 15 then the nitrosonium ion NO+ was created at some 16 point and that combined with the DMA to create 17 NDMA. 18 Is that your opinion? 19 A. That's the scheme I draw in the -- 20 in my report. 21 Q. And let's go now to page 61 of this, 22 61 of 236. 23 Looking at the bottom part of the 24 page.</p>

<p style="text-align: right;">Page 202</p> <p>1 A. I'm -- can you give me a second? I 2 just get to that page. Thank you. 3 Yes, I'm -- I'm with you now. 4 Q. This is part of the root cause 5 analysis for the TEA process with sodium nitrite 6 quenching. 7 Do you see that? 8 A. So we talk about that. 9 Q. Left column it says "TEA process 10 (with sodium nitrite quenching)"? 11 A. I'm sorry. So you talk about the 12 right column? 13 Q. Left column. 14 A. Oh, hold on. I lost it. 15 Q. It says "TEA process (with sodium 16 nitrite quenching)." 17 A. Oh, yeah. So the last column said 18 that, yes. 19 Q. And if you go to the right, it says: 20 Number 1. "Triethylamine 21 hydrochloride was used as catalyst. Sodium 22 nitrite was used for quenching after reaction." 23 You see that? 24 A. Yes, I do see that.</p>	<p style="text-align: right;">Page 204</p> <p>1 to read each sentence, right? So just now by 2 reading number 2, I had a puzzle. 3 Q. Have you ever seen this page before? 4 Do you know? 5 A. I cannot -- I cannot remember from 6 off my mind -- head, no. 7 Q. Looking now at page 61 of 236 of 8 this deviation investigation report where they're 9 talking about the TEA process with sodium nitrite 10 quenching, on the right-hand side it says: 11 "Number 3. "Triethylamine 12 hydrochloride may contain diethylamine and 13 dimethylamine, react with nitrous acid (formed by 14 sodium nitrite and hydrochloric acid) during the 15 next quenching reaction, and NDMA and NDEA may be 16 formed." 17 Is that an accurate statement as a 18 matter of chemistry? 19 A. Well -- 20 Q. Do you disagree with ZHP's analysis? 21 A. In term of chemistry, at the same of 22 what they say, if the TEA hydrochloride contain, 23 right? So there's an assumption. If this 24 catalyst used in this particular process, this</p>
<p style="text-align: right;">Page 203</p> <p>1 Q. It says: 2 Number 2. "No DMF solvent is added 3 in crude step, and no dimethylamine will be 4 degraded." 5 See that? Do you see what I just 6 read, number 2? 7 A. So number 2 is reading "No DMF 8 solvent is added in crude step, and no 9 dimethylamine was -- will be degraded." 10 Q. That's what I just read, correct? 11 A. By reading, that's correct, but that 12 doesn't make much sense to me, though. 13 Q. Have you ever seen what I'm showing 14 you right now? Have you ever seen this before? 15 A. Well, I see -- I read many things. 16 Q. Doctor, I understand you read a lot 17 of things. I'm asking if you read this. 18 MR. BERNARDO: He's trying to 19 answer your question. Please stop 20 interrupting him. 21 THE WITNESS: Yeah. 22 BY MR. SLATER: 23 Q. Okay. 24 A. I possibly did, but I just -- I need</p>	<p style="text-align: right;">Page 205</p> <p>1 particular step contain diethylamine and 2 dimethylamine, that's the assumption. If they 3 contain those, they can actually react with 4 nitrous -- nitrous acid, which is formed through 5 the sodium nitrite with hydrochloric acid. That's 6 correct. 7 Q. Let's go to 52 of 236, please. 8 Looking at the top of the page, this 9 says in part: 10 "Based on the investigation and the 11 evaluation of the route of synthesis, NDEA is most 12 likely formed in Step 4 crude stage, where toluene 13 is used as solvent and triethylamine hydrochloric 14 as catalyst for the tetrazole formation." 15 Do you see what I just read? 16 A. I think you read it right. 17 Q. Do you agree with that statement 18 that that's the most likely point in the process 19 when the NDEA was formed? 20 A. Based on the scheme that the -- 21 these people using, based on my knowledge of 22 chemistry, that is the step where NDEA was formed. 23 Q. It then says -- rephrase. 24 This report states:</p>

<p style="text-align: right;">Page 206</p> <p>1 "Specifically, triethylamine (TEA) 2 may contain trace amount of diethylamine as an 3 impurity." 4 Are you aware of that, that an 5 impurity of triethylamine can be diethylamine? 6 A. Well, I didn't -- I think you didn't 7 read it, the whole sentence. What I'm reading is 8 "Furthermore, triethylamine may be susceptible to 9 low level decomposition" -- 10 Q. I didn't -- I didn't read that 11 sentence because that's not what I asked you 12 about. It's a separate sentence. 13 I don't understand, Doctor. Can you 14 just stick with what my question, please? 15 A. Right. But I need to first 16 understand which sentence you are reading because 17 you are -- 18 Q. You didn't understand which sentence 19 I read? I read the sentence. I'll do it again. 20 I'm sorry. Let's -- let's try this again. 21 It states: 22 "Specifically, triethylamine (TEA) 23 may contain trace amount of diethylamine as an 24 impurity."</p>	<p style="text-align: right;">Page 208</p> <p>1 hypothetical, right? So I read those. Honestly, 2 that doesn't mean too much to me because they may 3 contain also means may not contain. 4 Q. What's your opinion? 5 Does -- does triethylamine 6 potentially contain trace amounts of diethylamine 7 as an impurity when it's purchased? 8 A. My con -- my opinion -- 9 Q. Do you have an opinion one way or 10 another on that question? 11 A. I don't know what ZHP bought, right? 12 I cannot judge whether any impurity, including 13 diethylamine was part of the TEA they bought, 14 right? But what I can say my opinion is, this 15 sentence really doesn't show anything really 16 specific. It says "may contain trace amount of 17 diethylamine." It also mean may not contain. 18 So I -- 19 Q. That's your reading of this? Okay. 20 That's fine. 21 A. Yeah. 22 Q. Now, I'm going to ask you again just 23 so we're clear. We move on. 24 Do you have an opinion as to whether</p>
<p style="text-align: right;">Page 207</p> <p>1 I want to ask you. 2 Are you aware that triethylamine may 3 contain a trace amount of diethylamine as an 4 impurity? Are you aware of that? 5 A. So where this -- 6 Q. Yes or no. 7 A. Where this sentence is? 8 Q. It's right in front of your face. I 9 just read it to you. Three lines down, it says: 10 "Specifically, triethylamine may 11 contain trace amount of diethylamine as an 12 impurity." 13 Do you see that? 14 A. In the first paragraph? 15 Q. Yes. 16 A. "Specifically, triethylamine may 17 contain trace amount of diethylamine as an 18 impurity." 19 Yes, I read that. Correct. 20 Q. Did you know that before I just read 21 it to you that diethylamine can be an impurity of 22 triethylamine? 23 A. Well, my read is triethylamine may 24 contain trace amount. So these statement are all</p>	<p style="text-align: right;">Page 209</p> <p>1 or not the triethylamine that was used by ZHP 2 potentially contained trace amounts of 3 diethylamine as an impurity? Yes or no. Do you 4 have an opinion on that or not? 5 A. I don't have opinion on that. 6 Q. This states: 7 "Furthermore, triethylamine may be 8 susceptible to low level decomposition under 9 certain conditions to produce trace amount of 10 diethylamine." 11 Do you see the sentence I just read? 12 A. I did. 13 Q. Do you have an opinion as to whether 14 or not the triethylamine was susceptible to low 15 level decomposition under certain conditions to 16 produce trace amount of diethylamine? 17 A. This sentence, again, is very vague. 18 That's like all hypothetic. "May be susceptible 19 to low level." All these words are doesn't really 20 show anything scientifically. 21 So I think I just say I don't have 22 any opinion on this. Because this is really 23 doesn't show anything that is scientific, right? 24 So it may make susceptible means possibility,</p>

<p style="text-align: right;">Page 210</p> <p>1 right? So -- or there is a chance, right? So I 2 don't see why this provide anything that's 3 specific. 4 Sorry. 5 Q. Do you see at the bottom of the 6 page. Let's scroll down just a tiny bit. 7 "Conditions for NDEA formation." 8 And you see it says: 9 "The presence of trace amount of 10 NDEA in the final Valsartan drug substance 11 requires the convergence of the following three 12 factors." 13 Do you see that? 14 A. You talk about the next bullet, 15 right? Number 3. "Conditions for NDEA 16 formation," right? 17 Q. Correct. 18 A. There's a bunch of Chinese and then 19 you read the first. You read the sentence in 20 between that "The presence of trace amount of NDEA 21 in the final Valsartan drug substance requires the 22 convergence of the following three factors." 23 Yes, I saw that. 24 Q. And the three factors:</p>	<p style="text-align: right;">Page 212</p> <p>1 between secondary amines and nitrite in the 2 presence of the target product." 3 That's the third factor listed, 4 right? 5 A. If you need to form the NDEA, this 6 is what you have to make the two things together. 7 That -- that just said nothing, but based on the 8 analysis from ZHP, what the potential. They 9 actually did the backward analysis. 10 If we know now this impurity is 11 formed, what are the required reagent. There are 12 two of them required to form this product, and 13 these two required species must be together. 14 So that's -- that's what they 15 actually do here. 16 Q. When they refer to "in the presence 17 of the target product," they're talking about the 18 fact that when the quenching takes place, the 19 target product is still present in the mixture, 20 right? 21 A. Can I read that sentence one more 22 time? So to understand what the target product 23 is? 24 "The possibility of direct" --</p>
<p style="text-align: right;">Page 211</p> <p>1 Number 1. "Presence of diethylamine 2 in the manufacturing process; such as its presence 3 in quenching step." 4 Do you see that? 5 A. I do. 6 Q. It doesn't matter how the 7 diethylamine got there. It just matters that it's 8 there, correct? 9 A. Well, as we just talk about 10 dimethylamine, right? So based off the knowledge 11 we learn so far and because right now we know NDEA 12 already form, this is a required reagent to get 13 NDEA formation. 14 Q. Second. "Presence of nitrous acid 15 in the manufacturing process, such as quenching of 16 azide using sodium nitrite." 17 So that's what they state is the 18 second factor, correct? 19 A. Right. To -- the same reason. To 20 make the NDEA as a product, you need two 21 reactions. So the second it talk about the 22 formation of the second reaction. 23 Q. Third it says: 24 "The possibility of direct contact</p>	<p style="text-align: right;">Page 213</p> <p>1 (reads document). 2 Yes. My -- my understanding is the 3 target product talk about the drug molecule. 4 Q. If ZHP had chosen to extract the 5 target product, the crude valsartan from the 6 mixture before quenching, then the product would 7 not have been contaminated with the nitrosamines 8 in either process, right? 9 A. So if I understand what you describe 10 is, you are saying if -- if ZHP decide to do the 11 extraction before you add the nitrite, right? 12 That's what you described? 13 Q. Correct. 14 A. If that's the case, no, you won't be 15 able to form. Based on this hypothesis, right? 16 These two other reactions. You need to see each 17 other. If you don't let them see other, you 18 don't -- before you actually purify a compound, 19 then you don't have a chance to form the product. 20 That's correct. 21 Q. Do you agree -- 22 MR. SLATER: You can take that 23 down, Chris, for now. Thanks. 24 BY MR. SLATER:</p>

<p style="text-align: right;">Page 214</p> <p>1 Q. Do you agree with me -- well, let me 2 ask it differently. 3 Do you have any understanding as to 4 whether or not ZHP was required to make every 5 feasible technical effort to prevent the formation 6 of genotoxic or carcinogenic compounds during the 7 drug substance synthesis and drug product 8 manufacturing for valsartan? 9 MR. BERNARDO: Object to the 10 form of the question. Vague. Compound. 11 Argumentative. 12 Go ahead, Dr. Xue. 13 THE WITNESS: Can you make 14 the question shorter? Because you have a 15 long question here. 16 BY MR. SLATER: 17 Q. Was ZHP required to make every 18 feasible technical effort to prevent the formation 19 of genotoxic or carcinogenic compounds during the 20 manufacture of valsartan? 21 MR. BERNARDO: Object to the 22 form of the question. Also, beyond the 23 scope of his report and area of 24 expertise.</p>	<p style="text-align: right;">Page 216</p> <p>1 Q. NDMA and NDEA. Those are genotoxic 2 compounds, right? 3 A. Yes, NDMA and NDEA they are. 4 Q. So if ZHP was required to make every 5 feasible technical effort to prevent the formation 6 of genotoxic or carcinogenic compounds such as 7 NDMA or NDEA, one of the things that they could 8 have done was to do scientific research, correct? 9 MR. BERNARDO: Object to the 10 form of the question. 11 BY MR. SLATER: 12 Q. I'm just asking. Could they -- 13 could they have done scientific research into that 14 subject? 15 A. I think the question is, it's very 16 vague because, as I mention just now, the 17 genotoxic or carcinogenic compound is very broad 18 concept. They are also related to the disease and 19 also dose and time. All these things. So it's 20 hard to -- for ZHP to decide what is the scope 21 they have to control. 22 Although I'm not a regulatory 23 scientist, I'm trying to answer here. 24 Yes, I put myself at the situation</p>
<p style="text-align: right;">Page 215</p> <p>1 THE WITNESS: I really hope I 2 can, but I honestly I'm not a regulatory 3 scientist. The requirement from FDA or 4 genotoxicity requirement, all these 5 things I'm not familiar with. 6 BY MR. SLATER: 7 Q. From the perspective of organic 8 chemistry, if an organic chemist who was involved 9 with these processes at ZHP was required to make 10 every feasible technical effort to prevent the 11 formation of genotoxic or carcinogenic compounds 12 as part of these processes, you would agree it 13 would have been feasible for them to do scientific 14 research, right? 15 MR. BERNARDO: Object to the 16 form of the question. Vague. Calls for 17 speculation. 18 THE WITNESS: So I'm not 19 quite clear what compound you talk about. 20 Because genotoxic compound I don't know. 21 I don't have a full list. I assume 22 there's hundreds, if not thousands, of 23 them. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 217</p> <p>1 to do research or to develop a drug. If you ask 2 me what I need to -- I absolutely need to, I want 3 to do everything that I can to control everything 4 to the best of what I can. 5 But what is the scope that I need to 6 be aware of, right? So that's the question. If I 7 don't know in my process of NDEA, NDMA, or any 8 other nitrosamine or any compound, right? That 9 is -- that is on the -- on the warning table or on 10 the genotoxic or carcinogenic list, I don't think 11 it's reasonable for -- for anybody to be required 12 to just go out to test everything on the list. 13 I don't -- I'm not, again, develop a 14 drug past FDA yet, but I know in my lab, we -- we 15 pretty much try to learn based on the knowledge or 16 science available to us and develop our risk 17 assessment. 18 If something happened, we go back 19 and do those root cause unless trying to fix 20 the -- the reaction so we don't -- we don't -- we 21 don't have this issue anymore. So that's the 22 practice. 23 I really don't think it's -- it's -- 24 it's reasonable to require a company when they --</p>

<p style="text-align: right;">Page 218</p> <p>1 they really don't -- they don't know what -- what</p> <p>2 is -- like you said, what -- what is the scope.</p> <p>3 What -- what -- what are the things on the radar</p> <p>4 they have to pay attention. If you don't know,</p> <p>5 how can I design something to avoid that?</p> <p>6 Q. One of the things they knew was what</p> <p>7 chemicals and solvents they were introducing into</p> <p>8 the process, right?</p> <p>9 A. I --</p> <p>10 Q. It's a yes-or-no question.</p> <p>11 Did they know what --</p> <p>12 A. For that I agree. They know what</p> <p>13 they use and they know --</p> <p>14 Q. Doctor, I asked a very simple</p> <p>15 question.</p> <p>16 Did the people at ZHP know what</p> <p>17 chemicals and substances they introduced into the</p> <p>18 manufacturing processes?</p> <p>19 A. They do know and I think --</p> <p>20 Q. So the answer is, yes, they knew?</p> <p>21 MR. BERNARDO: Let -- let him</p> <p>22 finish his answer.</p> <p>23 MR. SLATER: Well, maybe you</p> <p>24 could ask your expert when I ask him such</p>	<p style="text-align: right;">Page 220</p> <p>1 So you just ask me whether ZHP</p> <p>2 know what they use in there. My answer</p> <p>3 is, yes. But -- but whether they will</p> <p>4 know what's -- what's going to be</p> <p>5 available next decade about this</p> <p>6 compound, I will say, no, they probably</p> <p>7 don't know at this moment.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. Simple question.</p> <p>10 Did ZHP know what chemicals and</p> <p>11 substances were used in its manufacturing</p> <p>12 processes for valsartan? Yes or no.</p> <p>13 A. They know.</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 question.</p> <p>16 THE WITNESS: I'm sorry.</p> <p>17 MR. BERNARDO: Object to the</p> <p>18 form of the question asked and go on.</p> <p>19 THE WITNESS: My answer is,</p> <p>20 yes, they know based on the time and the</p> <p>21 knowledge around them.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. Were the chemists and the people at</p> <p>24 ZHP responsible to know that certain structural</p>
<p style="text-align: right;">Page 219</p> <p>1 a simple question, just answer it and not</p> <p>2 go on to a speech.</p> <p>3 MR. BERNARDO: He's qualifying</p> <p>4 his answer, which he's permitted to do,</p> <p>5 and you're jumping on top of his</p> <p>6 question. Let him just finish.</p> <p>7 THE WITNESS: Well, I -- yeah,</p> <p>8 I'm sorry if I went long.</p> <p>9 But you asked me whether ZHP</p> <p>10 knows what they put in their reaction</p> <p>11 vessel, my answer is, yes, they know.</p> <p>12 But you will ask me whether</p> <p>13 they should know every single thing about</p> <p>14 every single reaction of everything they</p> <p>15 add into their reaction vessel, that kind</p> <p>16 of requirement with my training as a</p> <p>17 scientist, I think that's a little too</p> <p>18 much.</p> <p>19 Because science is growing,</p> <p>20 right? Evolving, right? So we know</p> <p>21 certain compound have this character.</p> <p>22 That's our current knowledge. Next year</p> <p>23 or next decade that knowledge might</p> <p>24 expand, right?</p>	<p style="text-align: right;">Page 221</p> <p>1 groups, including N-nitroso-compounds such as NDMA</p> <p>2 and NDEA, were considered to have extremely high</p> <p>3 carcinogenic potency and that they were excluded</p> <p>4 from the threshold approach --</p> <p>5 MR. BERNARDO: Objection.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. -- about evaluation of impurities in</p> <p>8 drug substances?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question. Assumes facts.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Do you know whether they were</p> <p>13 supposed to know that or not?</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 form of the question. Assumes facts.</p> <p>16 Compound. Vague.</p> <p>17 Go on, Dr. Xue.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. It's a yes or no. Do you know</p> <p>20 whether they were supposed to know that or not?</p> <p>21 A. Well, in your question, you describe</p> <p>22 NDMA and NDEA as extremely toxic compound. For</p> <p>23 that I disagree because they are DNA modifiers.</p> <p>24 There are publications document about these</p>

<p style="text-align: right;">Page 222</p> <p>1 compounds to show they are potential or 2 probable -- probable cancer-causing -- causing 3 reagent, right? 4 So even FDA, they are not super 5 clear whether these are direct -- there is direct 6 evidence to show these particular compounds are 7 actually the direct cause of cancers. 8 So I don't think it's right at this 9 moment we characterize them as extremely toxic 10 cancer-causing compounds. 11 MR. SLATER: Let's go to the 12 FDA Guidance for Industry from December 13 2008. I guess that will be Exhibit 9. 14 MR. BERNARDO: And, Adam, when 15 you're at a point to break, we've been 16 going about an hour and 10 minutes and 17 I'd appreciate. 18 MR. SLATER: Well, I'm going 19 to ask a couple more questions about this 20 and then we can break. 21 MR. BERNARDO: All right. 22 (Document marked for 23 identification as Xue Exhibit 9.) 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 224</p> <p>1 or not ZHP needed to be vigilant to ensure that if 2 there were any such compounds as I just read in 3 that sentence produced as part of their 4 manufacturing process for valsartan that they 5 needed to identify them? 6 A. So that sentence you were just 7 reading, right, if I want to repeat what you just 8 read, there are some compound containing certain 9 chemical structures, structure groups. 10 So nitrosamine, as here it says 11 nitroso compound, that's what we discuss here, 12 right? It's -- it's a group of compound which 13 contains infinitive number of nitroso compound, 14 right? So that's like everything has a nitroso 15 group is called a nitroso compound. 16 Here you talk about there are 17 evidence to show some compound containing this. I 18 really don't think we can actually just say every 19 nitroso compound here. Okay? That -- 20 Q. Do you disagree with the FDA 21 guidance? 22 A. I disagree with what you 23 interpret -- interpret just now. I strongly 24 disagree.</p>
<p style="text-align: right;">Page 223</p> <p>1 Q. This is Exhibit 9. The FDA's 2 Guidance for Industry. "Genotoxic and 3 Carcinogenic Impurities in Drug Substances and 4 Products: Recommended Approaches" December 2008. 5 Have you ever seen this document 6 before? 7 A. I don't remember it particularly. 8 Q. Let's go to page 8. Top paragraph. 9 Blow it up a tiny bit. Okay. Perfect. 10 At the top of page 8, the last 11 sentence of the carryover paragraph says: 12 "However, there are some compounds 13 containing certain structural groups" and then in 14 parentheses "aflatoxin-like-, N-nitroso-, and 15 azoxy-structures) that have extremely high 16 carcinogenic potency and are excluded from the 17 threshold approach." 18 Do you see what I just read? 19 A. I saw what you just read. 20 Q. Did you know that before I just 21 showed that to you? 22 A. I don't remember reading the exact 23 same sentence, but I can see it now. 24 Q. Do you have an opinion as to whether</p>	<p style="text-align: right;">Page 225</p> <p>1 Because, again, as I wrote in my 2 report it's clear as a science -- as a scientist, 3 right? It's very clear to me when you actually 4 generalize any statement like this, you see 5 nitroso compound it's highly, extremely toxic. 6 That fundamentally is just not correct. 7 Because if you know, right, for any 8 nitroso compound to be -- to become a potential 9 DNA alkylator, a DNA modifier, you have to undergo 10 a process which include a type of enzyme called 11 P450, right? 12 That enzyme has to take the 13 substrate into its active site and every enzyme's 14 active site is very unique. It's not like 15 everything you can take get to the active site. 16 So there are very specific nitroso 17 compound that can be actually take into the active 18 site, and that can potentially. Even if you get 19 into the active site, it doesn't mean it can be 20 turned into an alkylating agent. 21 So it's really not fair to say a 22 nitroso compound because it's a nitroso compound 23 so it must be able to be turned into a DNA 24 alkylating agent.</p>

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1 Q. I didn't ask you that. You know,
2 what, Doctor? I didn't ask you that.
3 In fact, you're not a general
4 causation expert in this case, and with all due
5 respect, I don't need to hear from you general
6 causation testimony. That's not what I asked you.
7 Okay? So I'd appreciate not being given a speech
8 about whether you think that these substances are
9 dangerous or not or anything like that.
10 I'm reading from an FDA guidance and
11 asked you a different question which, with all due
12 respect, you didn't answer.
13 So I'm going -- I'm going to try it
14 again.
15 Do you have any opinion as to the
16 level of scientific research and analysis ZHP
17 needed to do to make sure that they identified any
18 N-nitroso-compounds that were created during the
19 manufacture of valsartan?
20 Yes or no. Do you have an opinion
21 as to level of research that they should have
22 done?
23 MR. BERNARDO: Object to the
24 form of the question and the commentary

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1 before, particularly in light of the
2 rephrasing of the question now.
3 MR. SLATER: You know what?
4 I'm going to withdraw the question. I'm
5 going to ask the court reporter to please
6 read back the question I asked before
7 that massive long question -- that long
8 answer that the witness just gave.
9 Because you're right. I
10 didn't rephrase it exactly the same way.
11 So let's go back to the question that
12 wasn't answered the first time.
13 (The reporter read the record
14 on page 224 lines 20-21.)
15 MR. SLATER: No, it was before
16 that.
17 THE WITNESS: I said I
18 disagree with that because --
19 MR. SLATER: Please, Doctor.
20 We're not asking you to say anything
21 right now.
22 MR. BERNARDO: Please don't
23 raise your voice at the witness.
24 MR. SLATER: I'm sorry, but

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1 you know what? If you were in my shoes,
2 you'd be just as frustrated.
3 MR. BERNARDO: I've been in
4 your shoes many times and I don't raise
5 my voice to the witness.
6 (The reporter read the record
7 on page 223 line 24 through page 224
8 line 5.)
9 MR. BERNARDO: Object to the
10 form of the question on the same ground.
11 Asked and answered, particularly in light
12 of the phraseology of that question and
13 the statements in the document.
14 BY MR. SLATER:
15 Q. It's a yes-or-no question. Do you
16 have an opinion or not?
17 A. I do have opinion. I said --
18 Q. Okay.
19 A. -- the way you --
20 Q. I didn't ask you what the opinion
21 was. I asked if you had an opinion.
22 A. I do.
23 Q. Okay. Do you -- is it your opinion
24 that ZHP had to be vigilant to make sure they

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1 identified any nitrosamines that were formed by
2 the processes, or is it your opinion they did not
3 need to be vigilant to try to identify
4 nitrosamines formed by the processes?
5 A. They do not --
6 MR. BERNARDO: Object to the
7 question.
8 THE WITNESS: -- because they
9 don't -- I'm sorry.
10 MR. BERNARDO: Object to the
11 form of the question. Vague.
12 Go on.
13 THE WITNESS: My opinion is
14 they do not because really they have no
15 reason to do any study.
16 This statement, as I
17 mentioned, you use this statement from
18 FDA, but you interpret this statement
19 totally wrong.
20 BY MR. SLATER:
21 Q. There was literature available --
22 and you said it in your report -- it was
23 documented that sodium nitrite applied to a
24 secondary amine could create NDMA or NDEA,

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1 correct? That was literature that was available
2 to ZHP, right?

3 A. My opinion for that is, it's for the
4 secondary amine to react with nitrosonium ion,
5 It's a documented reaction that is not common as
6 the expert of the plaintiffs claim every average
7 chemist should actually know that.

8 Q. It was a documented reaction such
9 that if the chemists at ZHP had done scientific
10 research, they would have been able to find that
11 reaction documented in the literature, correct?

12 A. I disagree.

13 Q. You're saying it's impossible for
14 them to find that in the literature that you told
15 me it's documented in?

16 MR. BERNARDO: Object to the
17 form of the question. The
18 characterization of his answer, and the
19 not allowing him to finish his answer.

20 THE WITNESS: I said that my
21 opinion for this on this topic is very
22 clear.

23 Yes, the reaction for
24 secondary amine to react with nitrosonium

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1 ion to form NDMA is documented, but it's
2 not as common as the expert on the
3 plaintiff side claim.

4 And for why I said it's rare,
5 because the reaction require a reagent
6 that's dimethylamine, which is not -- ZHP
7 didn't aware at all their process can
8 actually produce.

9 So we thought that reactant
10 you cannot possibly expect or foresee the
11 formation of NDMA.

12 Also, I am here as a
13 scientist. I did research on nitrous
14 oxide. I know nitrosonium ion can
15 actually be reactive. So I'm -- I'm not
16 average here anymore. So I know the
17 other part of the reactivity, right?

18 Even me, I don't know the
19 presence of dimethylamine. So I really
20 feel these two together that just, as I
21 concluded or I offer my opinion.

22 I never said there's no way
23 they can figure out this reaction is
24 documented, but the fact that they don't

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1 have a secondary amine in their reaction
2 as designed, and they don't have enough
3 resource to actually figure that out.

4 So it's not fair to expect ZHP
5 to kind of foresee this reaction happened
6 to form NDMA.

7 BY MR. SLATER:

8 Q. You're not saying it could not have
9 been figured out. You're just saying it would
10 have been hard to figure it out.

11 Is that what I understand you're
12 saying?

13 A. What I'm saying is, NDMA formation
14 from dimethylamine and nitrosonium ion is
15 documented but is not common as the expert of the
16 plaintiffs claimed. However, to make it extremely
17 hard is, the two reaction -- one of the two
18 reactant was not there, and ZHP didn't know and
19 not possibly reasonably be expect to know that
20 this dimethylamine can actually -- actually
21 present in their reaction vessel.

22 That's all what I actually offered
23 as my opinion.

24 Q. Are you saying it was impossible for

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1 ZHP to know that DMA was known as one of the
2 primary impurities of DMF?

3 MR. BERNARDO: Object.

4 BY MR. SLATER:

5 Q. Yes or no. Are you saying it was
6 impossible for them to know that?

7 MR. BERNARDO: Object to the
8 form of the question. Vague.

9 THE WITNESS: As a -- as a
10 scientist, right? So I never say
11 anything that is impossible. I like to
12 see experiment. I like to see data.
13 Everything is supported by data by the
14 science. If there is, you know, there's
15 always be ways.

16 I don't want to be exclusive
17 like must be, like some of the
18 plaintiffs' experts was claiming
19 everybody should know this. When you see
20 sodium nitrite, you must be doing this.

21 I just not trained to do that.

22 BY MR. SLATER:

23 Q. You're not trained to do that you
24 said? I didn't hear that.

<p style="text-align: right;">Page 234</p> <p>1 A. Yeah, I just not trained to be 2 generalize everything will be absolute on 3 anything. 4 Q. In terms of what the chemists at 5 ZHP -- well, let me ask you this. 6 Do you have -- you have no 7 understanding of what -- well, rephrase. 8 You don't know what the ZHP chemists 9 would have found if they did scientific research 10 into the potential formation of nitrosamine 11 impurities -- well, rephrase. 12 You don't know what the ZHP chemists 13 would have found if they did research the 14 potential impurities of DMF, the potential 15 degradation products of DMF, and the potential 16 impacts of using sodium nitrite in this process, 17 you don't know what they would have found because 18 they never did the research, right? 19 MR. BERNARDO: Object to the 20 form of the question. Compound. Vague. 21 Go on. 22 THE WITNESS: Yeah, I cannot 23 speculate what result if I don't do that. 24 I don't even know if I do something today</p>	<p style="text-align: right;">Page 236</p> <p>1 Sorry. 2 Q. Have you seen it before? 3 A. Yeah, I don't remember exactly, but 4 I think so. 5 Q. Let's go to page 7 of 23, please. 6 The part I want to focus on is the 7 paragraph at the top that says "In addition." 8 It's the second paragraph. 9 Do you see that? 10 A. Yes. 11 Q. At the top of the page it says: 12 "In addition, as reported in 13 'Theoretical Investigation of 14 N-nitrosodimethylamine Formation from Nitrosation 15 of Trimethylamine, Journal of Physical Chemistry 16 2010,' TEA could react with nitrous acid directly 17 to form NDEA without proceeding via the 18 intermediary of DEA. The reaction mechanism is as 19 follows." 20 Do you see that? 21 A. Yes, I do see that statement. 22 Q. Were you aware before right now that 23 ZHP concluded that the nitrous acid could directly 24 nitrosate the trimethylamine to form NDEA?</p>
<p style="text-align: right;">Page 235</p> <p>1 I didn't do yesterday what I would have 2 got. So I cannot speculate. 3 MR. SLATER: All right. We 4 can take a break now, actually. 5 MR. BERNARDO: Okay. Thank 6 you. 7 THE VIDEOGRAPHER: Time right 8 now is 2:54 p.m. We're off the record. 9 (Recess). 10 THE VIDEOGRAPHER: Time right 11 now is 3:08 p.m. We're back on the 12 record. 13 MR. SLATER: Okay. We're 14 going to put up the next exhibit. I 15 think it's Exhibit 10 we're up to. 16 (Document marked for 17 identification as Xue Exhibit 10.) 18 BY MR. SLATER: 19 Q. Looking on the screen, Exhibit 10, 20 this is a document titled "Investigation regarding 21 unknown impurity (genotoxic impurity) of Valsartan 22 API" and it's Version 3 of this report. 23 Do you see this document? 24 A. Yes, I do.</p>	<p style="text-align: right;">Page 237</p> <p>1 A. I read this page before, but I don't 2 think ZHP concluded this. They just cite this 3 reference here to see if that's a possible 4 mechanism. 5 Q. Do you think these deviation 6 investigation reports are just a series of 7 statements about what might have happened, or do 8 you think they're actually conclusions about what 9 likely occurred? 10 MR. BERNARDO: Object to the 11 form of the question. Vague. 12 THE WITNESS: They are a 13 bunch of conclusions. They all 14 conclusions, but scientifically to me 15 they are not conclusions. They are 16 speculation. So hypothesis. 17 I don't think ZHP or anybody 18 here experimentally ever validate whether 19 this scheme showing on the -- the PDF 20 that you showing me is there's any reason 21 this happened. 22 I don't remember exactly every 23 detail about this paper. This paper 24 published in 2010 was actually as the</p>

<p style="text-align: right;">Page 238</p> <p>1 title it's "Theoretical Investigation." 2 There is no experimental evidence to 3 provide whatsoever to support this at 4 all. 5 I don't want to look down at 6 any theoretical investigation because my 7 lab myself, we do theoretical 8 investigation for many of my projects. 9 So, but we always couple these theories 10 or we call hypothesis with experimental 11 proof. 12 So this is definitely 13 something you can hypothesize. And by 14 just looking at the drawing here, that 15 make some sense of why they push the 16 arrow here and going there. 17 And then they can actually 18 conclude with a -- with a hypothesis that 19 the reaction without intermediate can 20 actually theoretically go, but that other 21 than a scientific hypothesis, it doesn't 22 say anything about it. 23 BY MR. SLATER: 24 Q. When you pointed out that the title</p>	<p style="text-align: right;">Page 240</p> <p>1 actually happens when you experiment. 2 Is that what you're saying? 3 A. Normally it's not just one 4 experiment because to -- especially to prove a 5 mechanism like these authors trying to do, it's 6 not a trivial thing, right? So I tell you we do 7 these kind of research a lot, right? 8 So it's a -- it's a -- it's a very 9 well-dedicated desire of a whole series of 10 experiments. Because you cannot, unfortunately, 11 as a chemist, to capture any intermediate or 12 transition state or any of these species on the 13 way. You can only isolate the product to how you 14 actually design an experiment that you can use the 15 product you isolated to prove this arrows that you 16 draw would all be correct. 17 That's really a big chunk of science 18 in organic chemistry. So that's what I do, but 19 I'll say we probably don't have time to go through 20 the detail. But this is very, very difficult and 21 high-end things. You do need to have a lot of 22 experiment to prove one hypothesis -- hypothetical 23 mechanism. 24 Q. That's -- what you're talking about</p>
<p style="text-align: right;">Page 239</p> <p>1 is "Theoretical Investigation," that would be, in 2 other words, for someone like me to say this is 3 something that's potential. It's possible, right? 4 A. You can -- you can say that way. I 5 like to say because, again, I publish paper like 6 this, too, but not exact same topic. I publish 7 papers on theoretical calculation quite a lot. 8 Actually, these are usually -- when I publish, I 9 always have some experimental result there. I use 10 my theory to explain what's going on. 11 If I only have a theory, that, 12 unfortunately, to me I might be bias here because 13 I never publish this way. When I only have a 14 theory pictured in any publication say this is 15 what potentially can happen, I as a reader always 16 have a big question mark join after that title. 17 Say, yes, there's theory comes up, but let's wait 18 for years to -- to test this. 19 Q. So there may be a theoretical 20 possibility, a potential for a reaction to occur 21 like this. In order to determine whether or not 22 that is really going to happen, I think what you 23 said is you need to do an experiment. You need to 24 test that -- that potential outcome and see if it</p>	<p style="text-align: right;">Page 241</p> <p>1 would also be the process of risk assessment. If 2 you're doing a risk assessment of a manufacturing 3 process, like ZHP was doing, they if -- they 4 recognize something could potentially occur, they 5 would need to do experiments and multiple tests to 6 find out what's really happening. 7 Is that what you're saying? 8 A. I agree with you and not agree. 9 Because we -- I remember before the break, we kind 10 of discuss about this, right? 11 So as a scientist, you're going to 12 know what is your hypothesis. When I know my 13 hypothesis -- like these people, these authors, 14 like my lab we do, too, right? We have a theory. 15 We set it up and then we design experiment toward 16 that to prove -- or prove is wrong or right. So 17 it doesn't matter. But we desire experiment to 18 prove. 19 But that goal or that hypothesis we 20 call is number one important in your work. If we 21 don't know, like you just described for ZHP, right 22 now we learn NDMA and NDEA are there, right? 23 So, but before we talk about dozen 24 years ago when we don't know. It's really just</p>

<p style="text-align: right;">Page 242</p> <p>1 for me, as a scientist, I just cannot visualize 2 that.</p> <p>3 Q. This article existed in 2010 and was 4 actually written by people in Beijing, China, 5 correct?</p> <p>6 A. I honestly don't remember the 7 authors at all. I don't know. I usually don't 8 read their institutions where they publish, but, 9 yeah.</p> <p>10 Q. You would agree with me that a 11 thorough scientific search of the literature 12 should have turned up this article because they 13 knew at ZHP they were using triethylamine. They 14 knew that they were going to use tertiary amine.</p> <p>15 So there's no reason why they 16 wouldn't have found this article at least, right?</p> <p>17 MR. BERNARDO: Object to the 18 form of the question. Calls for 19 speculation. Vague.</p> <p>20 THE WITNESS: I'm not at ZHP. 21 I really cannot. I hope I can answer, 22 right?</p> <p>23 So if I -- I just be myself, 24 right? I tell you if I'm in their shoes</p>	<p style="text-align: right;">Page 244</p> <p>1 Q. That's the words on the page, right? 2 That's what the words on the page say?</p> <p>3 A. That are the words on the page that 4 you were reading correctly, too. But as I said --</p> <p>5 Q. I only asked you if that's what it 6 says.</p> <p>7 A. Okay. Those are the words by 8 reading from the document to describe the scheme 9 that they draw as a potential of mechanism.</p> <p>10 Q. If ZHP had seen this article back 11 when they were developing the TEA process with 12 sodium nitrite quenching and when they were 13 actually using it, if they wanted to test to see 14 whether or not the process was yielding NDEA, they 15 could have tested and they could have looked for 16 NDEA to see if it was being formed. They could 17 have done that if they had chosen to.</p> <p>18 That was something that was 19 technologically feasible, correct? If they wanted 20 to, they could have done that, right?</p> <p>21 I'm not asking you whether they 22 needed to or not.</p> <p>23 I'm asking you: If they chose to do 24 a test to see if there was NDEA, they could have</p>
<p style="text-align: right;">Page 243</p> <p>1 what I will do, right? So this is what I 2 will do if I do a search.</p> <p>3 I found this paper. In the 4 title, they do theoretical investigation. 5 I will quickly just scan through the 6 article.</p> <p>7 If -- again, this is just me. 8 I'm not saying I'm the best, but if I see 9 there's no proof of this theory, I skip 10 it. That's me.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. We know that when ZHP read the 13 article -- well, rephrase.</p> <p>14 We know that when ZHP described the 15 article in this report, they concluded based on 16 this article that TEA could react with nitrous 17 acid directly to form NDEA without proceeding via 18 the intermediacy of DEA.</p> <p>19 That's what it says in the report in 20 front of us, correct?</p> <p>21 MR. BERNARDO: Object to the 22 form of the question and the 23 characterization.</p> <p>24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 245</p> <p>1 done that and determined whether there was NDEA, 2 right?</p> <p>3 A. Well, I really here I thought -- if 4 this is me, I did a search, very thorough search. 5 I found this paper reading theoretical 6 investigation. I show this proposal scheme, and 7 then there's no evidence.</p> <p>8 Honestly, this is something -- I 9 don't want to look down to anybody's work, but 10 this is just, you know, things you draw can make 11 sense, right? Like in organic chemistry.</p> <p>12 I teach organic chemistry. I teach 13 high-level organic chemistry. Things like this, 14 as I said, I don't want to be, you know, 15 disrespectful for other people's work, but I will 16 say I will just skip. I won't take it too 17 seriously. That's me.</p> <p>18 And I think -- I think what ZHP 19 using, if I read it correctly, is when they found, 20 right? They found, okay, I have this issue now.</p> <p>21 Let's go back to -- to see what are the 22 possibilities. That's what they propose, one of 23 the possibilities.</p> <p>24 Q. If ZHP had wanted to test to see if</p>

<p style="text-align: right;">Page 246</p> <p>1 NDEA was being formed in the TEA with sodium 2 nitrite quenching process, it would have been 3 technologically feasible to do that. 4 The equipment existed to be able to 5 look for NDEA, right? They could have done that 6 if they wanted to, correct? 7 A. If -- yeah, if the hypothesis is up 8 there, I'm looking for NDEA the method. I don't 9 know whether the method is established, but like 10 you said, the technology, the treatment of should 11 be available. 12 Q. For example, LC-MS or GC-MS you can 13 look for NDMA with that and that's the type of 14 technology used to look for NDEA and NDMA, right? 15 MR. BERNARDO: Object to the 16 form of the question. Compound. 17 THE WITNESS: I disagree 18 because -- 19 BY MR. SLATER: 20 Q. Wait. All right. 21 You disagree that you use mass 22 spectrometry to look for NDEA and NDMA? 23 A. Well, I disagree because there are 24 methods available not just, right? So if you say</p>	<p style="text-align: right;">Page 248</p> <p>1 available, right? 2 A. I believe so because I personally 3 used them. 4 Q. Right. 5 And that was the technology that one 6 could use to look for NDMA and NDEA if you -- if 7 you wanted to in a substance. 8 That's the technology -- two 9 technologies that you can use for that purpose, 10 right? 11 A. Yes. If you have the compound, you 12 can always choose the available technologies, 13 GC-MS, LC-MS. As I said, I use LC and GC both. 14 LC is more feasible for my type of research. 15 Yeah. 16 Q. And did you see the documents 17 showing that ZHP actually was using mass 18 spectrometry technology throughout this time? 19 They were using it going back to at 20 least 2009 going through the 2010s up through the 21 time that this was disclosed in 2018. 22 You've seen some of those documents, 23 right? 24 MR. BERNARDO: Object to the</p>
<p style="text-align: right;">Page 247</p> <p>1 if GC-MS is a potential that I will use, I will 2 say, yes, I will definitely consider GC-MS as a 3 potential to do the analysis. I'm not saying 4 GC-MS is not a potential. 5 What I'm saying is, you cannot just 6 say, okay, so automatically when you have this 7 potential issue, if you already identified this is 8 some impurity, what is the best way? So, you 9 know, I cannot say GC-MS is the best way. You 10 have to look around to see what is out there, 11 right? 12 So I'm developing valsartan. What 13 about other companies do also valsartan? Are 14 they -- what they use. So if I don't -- if I 15 don't have any test, right, so I probably look 16 around and see what everybody else does, right? 17 So I will. That's my practice, 18 right? So I don't want to get myself inventing 19 something which is not like everybody else does. 20 Q. Just to be clear -- 21 A. Uh-huh. 22 Q. -- GC-MS and LC-MS technology 23 existed in 2010, 2011, all the way through. That 24 was technologic -- that was technology that was</p>	<p style="text-align: right;">Page 249</p> <p>1 form of the question. 2 THE WITNESS: There -- there 3 is a lot of documents I saw, and I did 4 remember a lot of document with GC or LC. 5 I believe I saw ZHP used mass spec as 6 their detector to do some experiments. 7 BY MR. SLATER: 8 Q. And let's go -- let's go to the next 9 page if we could, page 8 of 23. At the top. 10 Now, continuing with this deviation 11 investigation report, it says: 12 "Based on the above report and 13 research paper, since TEA, hydrochloride, sodium 14 azide and sodium nitrite were also used in 15 Valsartan (TEA process), NDEA in Valsartan (TEA 16 process) could not only be formed by reaction of 17 DEA and nitrous acid, but also by reaction of TEA 18 with nitrous acid directly, the updated 'Three 19 Factor Analysis' for Valsartan (TEA process) is as 20 follows." 21 Did you see what I just read? 22 A. I saw that first paragraph you just 23 read. I think you read it correct, too. 24 Q. And you see they revised their Three</p>

<p style="text-align: right;">Page 250</p> <p>1 Factor Analysis, which we talked about earlier in 2 the deposition. So now number 1 is "Use of TEA 3 hydrochloride in the process." 4 Do you see that? 5 A. I saw that. 6 Q. And then the second and third. 7 Number 2 is "Use of sodium nitrite 8 in the process of quenching." 9 And then the third factor is 10 "Quenching takes place in the presence of target 11 product and DEA/TEA." 12 Do you see that? 13 A. Yes, I do see both of them. 14 Q. So ZHP concluded that the creation 15 of NDEA in the sodium nitrite with -- in the 16 sodium nitrite quenching -- let me rephrase. I 17 got it backwards. 18 So you now see that ZHP concluded 19 that the creation of NDEA with the TEA with sodium 20 nitrite quenching process could occur just through 21 direct nitrosation of the TEA itself, and that's 22 what they documented here in their report. 23 You see that now, correct? 24 It's what I just showed you. That's</p>	<p style="text-align: right;">Page 252</p> <p>1 mechanism TEA could actually form through direct 2 reaction to get you NDEA experimentally showing 3 with a condition that ZHP been using for their TEA 4 process with quenching. 5 So my own opinion for that 6 particular reaction is, before ZHP and Novartis 7 and Solco, they as a team figured this out through 8 a bunch of teamwork, nobody ever know this 9 reaction under the condition that ZHP was 10 performing can actually take place. 11 Q. And as we discussed, if the chemists 12 at ZHP had come across the literature we just 13 talked about and this concept of nitrosating a 14 tertiary amine, the best way that they could have 15 answered the question of whether this could occur 16 in that manufacturing process would have been to 17 test to see if it was happening. 18 That would have been the best way to 19 get the definitive answer, right? 20 A. Well, there are few assumptions we 21 made here. One is ZHP did a search and find that. 22 So if they don't, if they don't realize or 23 hypothesize the potential formation of NDEA, I -- 24 I personally don't see the motivation why they go</p>
<p style="text-align: right;">Page 251</p> <p>1 the words on the page, correct? 2 A. By reading, that's what they were 3 hypothesizing. I won't say this is conclusion, 4 though. 5 Q. You agree it's possible that that 6 happened, right? 7 A. I don't agree. 8 Q. Okay. So you disagree with ZHP on 9 this point? 10 A. No, I not disagree with ZHP. The 11 paper they publish is really against my -- my -- 12 my knowledge. I -- I really cannot take that 13 scheme and then -- ZHP they may -- they may agree, 14 but I don't agree with that science at all. 15 Q. Did you do anything in your analysis 16 as an expert to prove or disprove what ZHP stated 17 on this page that I just read to you? 18 A. I did a search myself from 19 literature to see the reaction between tertiary 20 amines like TEA, for instance, is one simple 21 tertiary amine with nitrosative reagents like 22 nitrosonium ions, for instance. 23 I didn't see any simple -- any 24 single example to show that without a complicated</p>	<p style="text-align: right;">Page 253</p> <p>1 out for a search. Let's put it aside. 2 If they -- for some reason they had 3 the motivation to do the search, when they see a 4 few papers, including this paper, show up if they 5 happen to see that. I doubt whether they will see 6 it, but if they did like they eventually found it, 7 as I said, as me as a chemist, I read the paper. 8 I will not take it, you know, this there's no 9 evidence or experimental evidence at all happen. 10 I won't do anything for them. 11 So those two -- those two levels, I 12 really just don't see ZHP has a reasonable reason 13 to actually test NDEA in there. 14 Q. You referred to what you would do as 15 a chemist. 16 Do you have any understanding of 17 what the chemists who are working on a process 18 that's to manufacture massive quantities of this 19 substance to be sold around the world to be 20 ingested by humans, do you have an understanding 21 of what their obligation was and what level of 22 scientific analysis they were required to do? 23 Just asking the question. Do you know? 24 A. I --</p>

<p style="text-align: right;">Page 254</p> <p>1 MR. BERNARDO: Object to the 2 question. Asked and answered. 3 Go on. 4 THE WITNESS: Yeah, I 5 definitely aware the difference of myself 6 and the people who involved in master 7 production of APIs. 8 But I will say the principle 9 that we use for research is the same, and 10 I also want to point out that the 11 database that I use for literature search 12 is not just for academic researchers. 13 Where what I found as a 14 reference is actually available to all 15 the industry people, all the academic 16 people, or actually for you, too. If you 17 go there, right? So that's the same. 18 So I'm -- what I found with 19 this topic, TEA process with quenching, 20 is that there's almost nothing reported 21 about this project -- about this topic, 22 right? 23 I mention that in my report, 24 right? So you probably -- I do research</p>	<p style="text-align: right;">Page 256</p> <p>1 the company, they together as a team have 2 figured out. 3 BY MR. SLATER: 4 Q. Well, actually, Novartis wasn't 5 evaluating the TEA with sodium nitrite quenching 6 process, were they? 7 A. Well, they are a part of -- what I'm 8 saying is, they throughout back-and-forth 9 communications, all these knowledge were based on 10 that. And then eventually they happen to learn, 11 okay, there is actually NDMA -- sorry -- NDMA or 12 NDEA formation. 13 I apologize. That's my phone. 14 Q. Let's go up to the -- let's take 15 this down and go to the next exhibit, which will 16 be -- 17 A. Can I stop to stop that? 18 Q. Yeah, go ahead. We'll put up the 19 next document while you're doing that. 20 (Document marked for 21 identification as Xue Exhibit 11.) 22 BY MR. SLATER: 23 Q. Let's go to the first page first, 24 and this is Exhibit 11.</p>
<p style="text-align: right;">Page 255</p> <p>1 a lot, but you probably don't, right? 2 You go off other business. 3 But a common reaction if I see 4 a really average chemist that know this 5 reaction or of people in the industry who 6 know this reaction well, it's well known 7 like the expert of the plaintiff they 8 claim, usually if you search for those 9 reaction, you got thousands, tens of 10 thousands hits. 11 This particular reaction, TEA 12 react with whatsoever condition to form 13 NDEA. I mean, talk about any, any 14 mechanism, right? 15 So I did this search. 16 Unfortunately, only can -- can you really 17 feel like with two hands I can count how 18 many hits I got throughout the history. 19 That tells me how little it's known. 20 That's why I also said for 21 this reaction, my opinion is, nothing is 22 known and this condition, now we learn 23 through this case it's a new condition 24 that ZHP, Novartis, and the other part of</p>	<p style="text-align: right;">Page 257</p> <p>1 Okay. We've put up on the screen an 2 article that is titled "Nitrosative Dealkylation 3 of Some Symmetrical Tertiary Amines." 4 Do you see that? 5 A. I'm sorry. I -- it's 11, right? 6 I'm opening now. 7 Yes. 8 Q. And this is an article that was 9 published in 1979. That's what it says up on the 10 left column from when the download was made. 11 Published on January 1, 1979. 12 A. Okay. 13 Q. And you can actually go to the end 14 of the article if you don't believe me, and it 15 says received 13th of June 1978 at the end of the 16 article to show you this is 1979 that it's 17 published. Okay? 18 And if you look at the first 19 paragraph, it talks about the fact that in the 20 very middle of the paragraph or little further 21 down the middle, it says: 22 "More recently attention has been 23 directed to the public health aspects of the 24 nitrosation of tertiary amines and quaternary</p>

<p style="text-align: right;">Page 258</p> <p>1 ammonium compounds."</p> <p>2 Do you see that?</p> <p>3 A. Yeah, you read it right.</p> <p>4 Q. Then the next sentence says:</p> <p>5 "It has been shown that a wide</p> <p>6 variety of tertiary amines can react with nitrite</p> <p>7 in the pH range of 3 to 6.5 and temperature 37 to</p> <p>8 90 degrees to produce nitrosamines in varying</p> <p>9 yields."</p> <p>10 Do you see that?</p> <p>11 A. You read it right, too.</p> <p>12 Q. So you would agree with me that</p> <p>13 we've talked about at least a few articles now.</p> <p>14 There was literature out there available to ZHP</p> <p>15 that they could have found if they had looked</p> <p>16 indicating that there was the potential for this</p> <p>17 reaction and the reactions in the sodium nitrite</p> <p>18 quenching TEA process to create a nitrosamine.</p> <p>19 There was -- that literature was</p> <p>20 available to show them this is something that</p> <p>21 could potentially happen under certain</p> <p>22 circumstances, correct?</p> <p>23 A. By reading that paragraph the author</p> <p>24 wrote, you're reading is definitely correct.</p>	<p style="text-align: right;">Page 260</p> <p>1 '80s, there's a big confusion or</p> <p>2 people -- not confusion.</p> <p>3 When they report, they</p> <p>4 actually put aniline, which is aromatic</p> <p>5 amino group belong to tertiary amines.</p> <p>6 So many of examples in these papers they</p> <p>7 are actually citing actually -- actually</p> <p>8 having is not truly trialkylamines like</p> <p>9 TEAs or DMAs or these -- these amines.</p> <p>10 Instead they actually talk</p> <p>11 about anilines. So anilines and real</p> <p>12 trialkyl tertiary amines are totally</p> <p>13 different family of compound in terms of</p> <p>14 their consistency because they have</p> <p>15 different PKAs.</p> <p>16 And that's why, right, so</p> <p>17 these authors -- that's my second</p> <p>18 point -- point out. So as the peak range</p> <p>19 for this reaction is also very critical.</p> <p>20 They didn't see anything like 1 or 2 or</p> <p>21 even 2 to 3. They specify saying 3 to</p> <p>22 6.5 because that's -- that's -- you see</p> <p>23 it's just a range of pH, but that's</p> <p>24 actually not.</p>
<p style="text-align: right;">Page 259</p> <p>1 Q. And, again, if ZHP had done that</p> <p>2 research, found this literature, if they wanted to</p> <p>3 know if this was a problem or an issue with their</p> <p>4 manufacturing process, they could have run</p> <p>5 straightforward testing to determine whether or</p> <p>6 not NDEA was being created.</p> <p>7 That was something they could have</p> <p>8 done in response to this literature, right?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question. Vague.</p> <p>11 THE WITNESS: I think there</p> <p>12 are two things. One is if you by just</p> <p>13 reading what -- what this literature</p> <p>14 said, right?</p> <p>15 So it says "attention has been</p> <p>16 directed to the public health aspects of</p> <p>17 the nitrosation of tertiary amines and</p> <p>18 quaternary ammonium compounds," and</p> <p>19 there's really not much.</p> <p>20 They also have a few citations</p> <p>21 there, but these paper, I cannot say I</p> <p>22 read every single paper of this field.</p> <p>23 That's not fair. I try to.</p> <p>24 So back then in the '70s or</p>	<p style="text-align: right;">Page 261</p> <p>1 If you read this reference</p> <p>2 when they talk about the tertiary amine,</p> <p>3 unfortunately, they are not really</p> <p>4 tertiary amine. They are aniline</p> <p>5 analogs. These compound under this range</p> <p>6 of pH will stay neutral. What I mean --</p> <p>7 I probably go through too much technical.</p> <p>8 You actually have the nitrogen</p> <p>9 stay neutral. You maintain the</p> <p>10 reactivity. That's how you actually.</p> <p>11 All these connected studies in this paper</p> <p>12 listed all make sense because you have</p> <p>13 the activity there.</p> <p>14 However, the real tri --</p> <p>15 tri -- trialkylamines or tertiary amines</p> <p>16 like a TEA or DMA, they are not. Their</p> <p>17 PK is much higher, right?</p> <p>18 Under this particular</p> <p>19 condition, they will not be able to</p> <p>20 react. That's why people also point out</p> <p>21 in papers, publications, say, wait, wait,</p> <p>22 wait.</p> <p>23 If you have these particular</p> <p>24 aniline-like compound they could react</p>

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1 but they have a real trialkylamine or
2 tertiary amine, they won't react. The
3 range of the pH is critical here.
4 So if I see this, I would say
5 ZHP that is using for their printing
6 process, which if I remember correctly is
7 3 or below, right? They -- they use
8 their strong acid to quench it to below
9 3. So that's -- that's the range 3D
10 printer TEA at least on theory.
11 I'm not trying to say that at
12 this -- at today we don't form NDEA.
13 Yes, we do have NDEA formed. I said
14 earlier, right, this is a really great
15 example to show that, okay, the teamwork
16 actually identified this particular
17 condition for the -- for this reaction
18 generate NDEA. That's the result.
19 But, I mean, all these
20 evidence that you show, it doesn't
21 support at all to show that there's a
22 chance for the reaction to take place.
23 BY MR. SLATER:
24 Q. When you're looking at these

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1 articles --
2 A. Uh-huh.
3 Q. Well, rephrase.
4 Do you think that the people at ZHP
5 should have looked at literature like this? If
6 they had actually looked for it and found it and
7 said, well, let's find all the reasons why this
8 article doesn't raise a risk so we don't have to
9 do a test?
10 Or do you think as a matter of risk
11 assessment they should have said, you know what?
12 These are potential reactions in general. Let's
13 be sure that it's not going to happen with this
14 process so that we're positive that this genotoxic
15 impurity is not being formed.
16 Wouldn't the better practice be as
17 risk assessment to be conservative and careful and
18 actually run the test based on literature like
19 this?
20 MR. BERNARDO: Object to the
21 form of the question.
22 THE WITNESS: Risk assessment
23 is definitely something we need to be
24 very careful, right? So everybody do

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1 research be very careful with reactions.
2 But as I said, the back-and-forth, the
3 hypothesis is important. What am I
4 facing if I don't know? Like ZHP, they
5 don't know on their radar NDEA for this
6 case in their TEA process with quenching
7 is a potential.
8 I just don't feel that's
9 reasonable to expect that.
10 BY MR. SLATER:
11 Q. Did you -- I'm sorry. I didn't mean
12 to interrupt you.
13 Do you think that they should have
14 known there was a risk of NDEA before they went
15 and did their literature search? Is that your
16 testimony?
17 A. My opinion was they don't know, and
18 there's no reason for them to know this reaction
19 can take place. So they didn't take any action,
20 right?
21 Q. And they didn't do any research
22 because they didn't know.
23 Is that what you're saying?
24 Your understanding is because -- let

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1 me ask it clean.
2 A. Right.
3 Q. Your understanding is because they
4 didn't know at the starting point that there was a
5 risk of NDEA or NDMA, they didn't need to do -- go
6 do scientific research to determine whether there
7 was a potential issue?
8 MR. BERNARDO: Object to the
9 form of the question.
10 BY MR. SLATER:
11 Q. Is that what you're telling me?
12 MR. BERNARDO: Vague. Asked
13 and answered.
14 THE WITNESS: I really don't
15 know what else I can add, right? So
16 it's --
17 BY MR. SLATER:
18 Q. Well, it's a yes-or-no question.
19 Maybe you can say yes or no as to whether I'm
20 right or not in understanding your opinion.
21 I'm not looking for a speech.
22 I just want to know yes or no; is
23 that correct?
24 A. My opinion is they don't know.

<p style="text-align: right;">Page 266</p> <p>1 That's -- that's clear. I want to make it very 2 clear. They don't know. 3 And second, there's almost no reason 4 or there's no reason for them to -- for us to 5 expect them to know back then, right? 6 So now, of course, in the year 2020 7 or even 2018 you figure out. After you figure 8 out, it's easy to explain. But before you figure 9 out, back then when they actually developed these, 10 I just don't feel it's fair for anybody to be 11 expected to -- to know everything about the 12 future. 13 Q. All right. You understand that 14 these scientists and people at ZHP were not just 15 doing theoretical evaluation of the literature. 16 Well, rephrase. 17 You understand that what we're 18 talking about here is a risk assessment for a 19 manufacturing process for a drug that's going to 20 then go into the human body. 21 You understand we're talking about a 22 risk assessment, right? Just yes or no. Do you 23 understand we're talking about -- 24 A. Yes, I do understand we talk about</p>	<p style="text-align: right;">Page 268</p> <p>1 impurities from the chemicals and substances in 2 that process? 3 I'm not asking if they had to rule 4 out every genotoxic impurity on earth. 5 But did they have to at least assess 6 for the risk of genotoxic impurities from the 7 potential reactions of the chemicals that they 8 were mixing together in that process? 9 Yes or no. Do you have an 10 understanding of whether they were required to do 11 that? 12 MR. BERNARDO: Object to the 13 form of the question. Asked and 14 answered. 15 THE WITNESS: I don't -- 16 BY MR. SLATER: 17 Q. Yes or no. 18 A. I don't think they're required to do 19 that because although you kind of -- 20 Q. That's fine. You said you don't 21 think so. Okay. Got it. 22 Looking at the article. 23 A. Yes. 24 Q. At the top, there's a little summary</p>
<p style="text-align: right;">Page 267</p> <p>1 risk assessment. 2 Q. And you understand, as I showed you 3 before, the risk assessment needed to ensure that 4 there were no unidentified genotoxic impurities. 5 You understand that was one of the things they 6 needed to do. 7 Do you accept that that's part of 8 the purpose of the risk assessment they had to do? 9 Yes or no. 10 MR. BERNARDO: Object to the 11 form of the question. 12 THE WITNESS: I don't 13 think -- I don't agree that they have to 14 assess every single potential genotoxic 15 compound because there's -- I don't -- I 16 don't -- I don't know. Tell me if there 17 are people doing that. 18 BY MR. SLATER: 19 Q. I didn't ask that. That's not what 20 I asked you. So I'll be clearer. 21 The risk assessment for these 22 manufacturing processes that are at issue, do you 23 accept that the risk assessments needed to take 24 into account the potential creation of genotoxic</p>	<p style="text-align: right;">Page 269</p> <p>1 and in the third line it says: 2 "The rate of formation of 3 diethylnitrosamine was found to be first order in 4 nitrous acid, triethylamine, and in the hydrogen 5 ion concentration for pH greater than 3.1." 6 You see that? 7 A. I'm sorry. I didn't see that. 8 Which paragraph we talk about here? 9 Q. At the top above, just below the 10 list of authors. 11 A. Oh, okay. That's the abstract. 12 Okay. 13 Q. And then it says: 14 "Rates increased with decreasing 15 amine basicity." 16 You see that? 17 A. I saw that, too. 18 Q. So you -- you were talking about -- 19 before about, in general, about tertiary amines? 20 A. Yeah. 21 Q. They're actually talking about 22 triethylamine here. 23 You see that they actually are 24 talking about triethylamine, right?</p>

<p style="text-align: right;">Page 270</p> <p>1 You see the word "triethylamine,"</p> <p>2 right?</p> <p>3 A. The word -- yeah. Because just now</p> <p>4 when you're reading, I didn't read the -- the</p> <p>5 abstract. I'm reading the abstract. Excuse me.</p> <p>6 (Reviews document.)</p> <p>7 Yes. Now I read that sentence.</p> <p>8 What was your question?</p> <p>9 Q. Before you were talking about</p> <p>10 tertiary amines in general and what this article</p> <p>11 means.</p> <p>12 I just was pointing out you would</p> <p>13 acknowledge they're talking about in part</p> <p>14 triethylamine. That's part of the analysis</p> <p>15 they're doing here.</p> <p>16 It's referenced there, correct?</p> <p>17 A. Yes, that -- that by reading, that's</p> <p>18 what they mention here.</p> <p>19 Q. And for the chemists at ZHP, if they</p> <p>20 had come across this or the other similar</p> <p>21 literature that points out that triethylamine can</p> <p>22 be nitrosated, as a matter of risk assessment and</p> <p>23 protecting the health and safety of patients, the</p> <p>24 reasonable thing to do would be to say, let's just</p>	<p style="text-align: right;">Page 272</p> <p>1 regarding the potential risks with using these</p> <p>2 various chemicals and found this literature, this</p> <p>3 article and similar articles in the literature</p> <p>4 that are out there, and recognized the potential</p> <p>5 nitrosation of triethylamine, the prudent thing to</p> <p>6 do would have been just to test for NDEA and NDMA</p> <p>7 just to make sure it wasn't being formed.</p> <p>8 That would be the prudent thing to</p> <p>9 do with this process that they had just developed</p> <p>10 to develop drug products to be put in people's</p> <p>11 bodies, right? That's why they're doing the risk</p> <p>12 assessment, to protect patient safety, right?</p> <p>13 Or don't you have an opinion?</p> <p>14 A. (Reviews document.)</p> <p>15 Yeah. My opinion is they really</p> <p>16 don't know this. They -- they --</p> <p>17 Q. My question assumed that if they</p> <p>18 found this literature.</p> <p>19 If they actually had done the</p> <p>20 research they didn't do and found that there's a</p> <p>21 potential creation of NDEA or NDMA, wouldn't the</p> <p>22 prudent thing to do in a risk assessment to</p> <p>23 protect the safety of patients being to do the</p> <p>24 test to see if it was producing those</p>
<p style="text-align: right;">Page 271</p> <p>1 test for nitrosamines just to make sure they're</p> <p>2 not being formed.</p> <p>3 That's the prudent thing to do,</p> <p>4 correct?</p> <p>5 MR. BERNARDO: Object to the</p> <p>6 form of the question.</p> <p>7 THE WITNESS: No, that's not.</p> <p>8 So we said you have to first -- you have</p> <p>9 to first look for nitrosamine. You know</p> <p>10 nitrosamine is a potential. That's --</p> <p>11 you made the assumption for granted,</p> <p>12 right?</p> <p>13 So we keep going back and</p> <p>14 forth. They don't have this information</p> <p>15 in their mind. Nobody ever done this,</p> <p>16 right? So they don't know this can</p> <p>17 possibly be -- be happening.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. I just asked you if -- but you're</p> <p>20 not -- you're not focusing on my question, with</p> <p>21 all due respect.</p> <p>22 If they had actually done research</p> <p>23 into the potential side effect -- rephrase.</p> <p>24 If they had done the research</p>	<p style="text-align: right;">Page 273</p> <p>1 nitrosamines?</p> <p>2 Wouldn't that be the prudent thing</p> <p>3 to do?</p> <p>4 A. Your assumption was this paper,</p> <p>5 right? So I --</p> <p>6 Q. Right.</p> <p>7 So assume for purposes of my</p> <p>8 question that they found this or similar</p> <p>9 literature alerting them to this potential risk.</p> <p>10 If they knew that potential risk,</p> <p>11 you would agree that then they should do tests to</p> <p>12 see if it happened, right?</p> <p>13 A. Well, the condition that here even</p> <p>14 if they -- like, first of all, I don't think they</p> <p>15 -- my opinion is solid, okay? I don't want to,</p> <p>16 you know, change or anything.</p> <p>17 This is they don't know there is</p> <p>18 NDEA formation. You -- you are setting the state</p> <p>19 saying, okay, they found this paper, while they're</p> <p>20 reading this paper.</p> <p>21 That's -- that's not happening,</p> <p>22 right? So they cannot find this paper.</p> <p>23 Q. I'm allowed to ask you hypothetical</p> <p>24 questions, Dr. Xue. Okay?</p>

<p style="text-align: right;">Page 274</p> <p>1 A. Okay.</p> <p>2 Q. We can all agree they did no</p> <p>3 research. They made no effort to learn about the</p> <p>4 potential risks associated with using these</p> <p>5 chemical substances. We already know that.</p> <p>6 I'm asking you to assume they</p> <p>7 actually did do the research and did find</p> <p>8 literature that indicated that the triethylamine</p> <p>9 could be nitrosated.</p> <p>10 In that event, the prudent thing to</p> <p>11 do as part of a risk assessment to protect patient</p> <p>12 safety would be to run a test and see if it was</p> <p>13 happening here, right?</p> <p>14 MR. BERNARDO: Object to the</p> <p>15 form of the question.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Wouldn't that be the smart thing to</p> <p>18 do?</p> <p>19 Wouldn't that have been the smart</p> <p>20 thing to do because then they never would have had</p> <p>21 this problem because they would have found the</p> <p>22 NDEA and this never would have happened?</p> <p>23 MR. BERNARDO: Object to the</p> <p>24 form of the question. Calls for</p>	<p style="text-align: right;">Page 276</p> <p>1 chemists at ZHP -- well, rephrase.</p> <p>2 If we assume the chemists at ZHP had</p> <p>3 actually done scientific research and had actually</p> <p>4 found this article, your -- your understanding of</p> <p>5 their obligation in doing a risk assessment for</p> <p>6 potential genotoxic impurities is to look at the</p> <p>7 article and say, well, it's not describing the</p> <p>8 exact conditions of our process. So we don't have</p> <p>9 to worry about it and we don't have to test it.</p> <p>10 Is that your understanding of what a</p> <p>11 reasonable risk assessment is?</p> <p>12 MR. BERNARDO: Object to the</p> <p>13 form of the question. Assumes facts.</p> <p>14 Argumentative. Calls for speculation.</p> <p>15 THE WITNESS: Right. As I</p> <p>16 said, it's a -- it's a hypothetical</p> <p>17 question, right? So it's a question that</p> <p>18 this paper, also the condition here, even</p> <p>19 this paper describe this is not the same</p> <p>20 as what they actually use in this piece</p> <p>21 conditions.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. I just said that.</p> <p>24 A. Right.</p>
<p style="text-align: right;">Page 275</p> <p>1 speculation. Assumes facts.</p> <p>2 THE WITNESS: Yeah. Although</p> <p>3 you said you are allowed to ask me</p> <p>4 hypothetical questions, I really -- I</p> <p>5 cannot answer hypothetical questions.</p> <p>6 So you said the stage start</p> <p>7 there and plus. So I say if you read</p> <p>8 that condition, they actually talk about</p> <p>9 here. They clearly say in their first</p> <p>10 paragraph it's 3 to 6 and a half and that</p> <p>11 there's a reason. I explain just now why</p> <p>12 those can actually take place, right?</p> <p>13 So and now, yes. So they --</p> <p>14 when they talk about the TEA, if we</p> <p>15 really want to discuss this, I need time</p> <p>16 to read the whole paper. I don't</p> <p>17 remember much of the detail of this</p> <p>18 paper, but -- but I can tell you that by</p> <p>19 just reading the -- the part, they're</p> <p>20 talking about the -- the pH value is</p> <p>21 greater than 3.1. That's their -- but</p> <p>22 that's their study were performed.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. So is it your opinion that when the</p>	<p style="text-align: right;">Page 277</p> <p>1 Q. What I asked you is: So you -- is</p> <p>2 it your opinion that in doing the risk assessment,</p> <p>3 the chemists should look and say, well, it's not</p> <p>4 the exact conditions of our process. So we don't</p> <p>5 have to worry about it and we shouldn't assess and</p> <p>6 make sure there's no NDMA.</p> <p>7 That's what your opinion is?</p> <p>8 If you see that there's potential</p> <p>9 nitrosation, if the article doesn't replicate the</p> <p>10 conditions of the process, you should just say,</p> <p>11 okay, nothing to worry about. We don't need to</p> <p>12 test?</p> <p>13 MR. BERNARDO: Same</p> <p>14 objections.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Is that your opinion?</p> <p>17 A. (Reviews document.)</p> <p>18 Yeah, if I -- as you point out,</p> <p>19 right? If ZHP, they happen to know this paper and</p> <p>20 then they read this paper, yeah. As I said, I</p> <p>21 still find this condition is -- is very different</p> <p>22 or significantly different because the condition</p> <p>23 they run, all these tests are different to what</p> <p>24 actually the quenching process of TEA with</p>

<p style="text-align: right;">Page 278</p> <p>1 quenching API process. I won't.</p> <p>2 Q. If the ZHP chemists --</p> <p>3 A. Uh-huh.</p> <p>4 Q. -- were aware in general that the</p> <p>5 triethylamine could be nitrosated by sodium</p> <p>6 nitrite, if they knew that in general, the prudent</p> <p>7 thing to do as part of the risk assessment to</p> <p>8 protect patient safety would be to do a test to</p> <p>9 make sure it's not creating a nitrosamine.</p> <p>10 That would be the prudent thing to</p> <p>11 do, wouldn't it be?</p> <p>12 MR. BERNARDO: Object to the</p> <p>13 form of the question. Vague.</p> <p>14 THE WITNESS: Yeah, it's</p> <p>15 hypothetic, right? So you, again, say if</p> <p>16 they know this already, but they don't</p> <p>17 know.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Well, I didn't say "if they know</p> <p>20 this already."</p> <p>21 I said if they knew of the potential</p> <p>22 for the sodium nitrite to nitrosate the</p> <p>23 triethylamine.</p> <p>24 In general, if they knew it could</p>	<p style="text-align: right;">Page 280</p> <p>1 mass production that they wouldn't need to do it</p> <p>2 either?</p> <p>3 MR. BERNARDO: Object to the</p> <p>4 form of the question. Vague.</p> <p>5 THE WITNESS: I'm not saying</p> <p>6 that. I say everything as a scientific</p> <p>7 project, we have a scope. We have based</p> <p>8 on the knowledge that we learn, we try to</p> <p>9 test the scope. What are the potentials,</p> <p>10 right? We know these are possibles.</p> <p>11 But you cannot force people to</p> <p>12 even consider the ones that to them are</p> <p>13 not possible. I think that's -- that's</p> <p>14 just not fair anymore.</p> <p>15 MR. SLATER: Let's go to</p> <p>16 another article. Let's to the</p> <p>17 theoretical investigation article.</p> <p>18 Have we shown that already or</p> <p>19 is this a new exhibit?</p> <p>20 Okay. So Exhibit I think it's</p> <p>21 12.</p> <p>22 (Document marked for</p> <p>23 identification as Xue Exhibit 12.)</p> <p>24 THE WITNESS: Can I go back?</p>
<p style="text-align: right;">Page 279</p> <p>1 happen under certain circumstances, there would be</p> <p>2 no reason for them not to do a test to make sure</p> <p>3 it wasn't happening here, correct?</p> <p>4 A. For me, I just don't see. It's like</p> <p>5 see -- you said if they say if they have the</p> <p>6 potential. I'm -- like me, I never heard about</p> <p>7 this reaction in my life before I be involved in</p> <p>8 this.</p> <p>9 If you tell me there's a potential.</p> <p>10 Every day every reaction has a potential, right?</p> <p>11 So how can I just because I hypothetically think</p> <p>12 about some potential?</p> <p>13 And if you're going to go back to do</p> <p>14 a risk assessment on every potential, again I'm</p> <p>15 running labs. I'm running project. I just don't</p> <p>16 feel that's reasonable to let my students go into</p> <p>17 the lab and running, I mean, think about any</p> <p>18 potential things that can happen. Potential.</p> <p>19 There is everything has, you know, infinitive</p> <p>20 potentials.</p> <p>21 Q. So you're saying because you</p> <p>22 wouldn't do that and you wouldn't require that in</p> <p>23 your lab, you would assume it wouldn't be required</p> <p>24 for process chemists at ZHP developing a drug for</p>	<p style="text-align: right;">Page 281</p> <p>1 MR. SLATER: You tell me,</p> <p>2 Chris. It's 12.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. So we're now going to put up as</p> <p>5 Exhibit 12, the "Theoretical Investigation --</p> <p>6 A. I'm still.</p> <p>7 Q. -- of N-nitrosodimethylamine</p> <p>8 Formation from Nitrosation of Trimethylamine."</p> <p>9 Do you see that?</p> <p>10 A. Hold on. I'm still loading.</p> <p>11 Q. Okay.</p> <p>12 A. Yes, it show up on my screen.</p> <p>13 Q. And if you look at this article,</p> <p>14 which is published in the Journal of Physical</p> <p>15 Chemistry in 2010 from the American Chemical</p> <p>16 Society, let's look at the Introduction.</p> <p>17 Can you blow it up, please?</p> <p>18 Perfect.</p> <p>19 And in the Introduction, if we go to</p> <p>20 the second paragraph. It's okay.</p> <p>21 The second paragraph says in part, I</p> <p>22 want to focus on the part that I want to talk</p> <p>23 about.</p> <p>24 In the middle of the paragraph,</p>

<p style="text-align: right;">Page 282</p> <p>1 there's a sentence that says "In addition." 2 It's about five or six lines down. 3 Do you see that? 4 "In addition to secondary amines, 5 however, a wide variety of tertiary amines have 6 also been demonstrated to react with nitrous acid 7 to produce N-nitrosamines in aqueous solutions." 8 Do you see that sentence? 9 A. Are you talking about the left 10 column? 11 Q. Yes. 12 A. Or the right? 13 Left column. You said the second 14 paragraph? 15 Q. Yes. 16 A. Okay. So I'm reading. 17 Q. In the middle of the second 18 paragraph under the Introduction on the left 19 column, it says: 20 "In addition to secondary amines, 21 however, a wide variety of tertiary amines have 22 also been demonstrated to react with nitrous acid 23 to produce N-nitrosamines in aqueous solutions." 24 Do you see that sentence?</p>	<p style="text-align: right;">Page 284</p> <p>1 sentence, right? 2 Q. Yes. 3 A. Let me see this article. 4 (Reviews document.) 5 Yeah. Under those two assumptions, 6 if I really specifically coming to look at this 7 paper, right? Which I don't think they will, 8 these people, too, because, again, there's no 9 motivation for them and this is hypothetical, 10 right? 11 But let's say if they found this 12 paper and if they read this paper, if I -- I was 13 ZHP chemist, I read this paper again. This is -- 14 I don't know whether this is same paper, but this 15 is a theoretical Investigation of -- of 16 nitrosodimethylamine from which NDMA formation 17 from nitrosation of triethylamine, right? 18 So this article tells me that, oh, 19 this paper was solely on this simple -- actually 20 structure, that's the simplest tertiary amine is 21 triethylamine. So they do some theoretical 22 investigation on this simple structure of the -- 23 the amines. That -- that -- that's really not 24 relevant to what I'm doing if I'm ZHP.</p>
<p style="text-align: right;">Page 283</p> <p>1 A. Yes, and I will read it. 2 Q. The creation of NDEA and NDMA in the 3 TEA with sodium nitrite quenching process occurred 4 in aqueous solution, correct? 5 A. Correct. 6 Q. This sentence -- well, rephrase. 7 If the science -- if the chemists -- 8 rephrase. 9 If the chemists at ZHP had come 10 across this article back when they were developing 11 or using that manufacturing process and had seen 12 that sentence, should that have been alerted them, 13 this is a potential reaction that we should risk 14 assess for to make sure it's not happening? 15 Would you at least agree with regard 16 to that sentence that would be enough to say, 17 okay, let's do a risk assessment and see if that's 18 actually occurring here? Because if it is, it's 19 not a good thing and we need to make sure it's not 20 happening? 21 A. Well, there is -- there is a quite a 22 few assumptions, right? You said if they did a 23 literature search, found this article and also if 24 they read the -- the Introduction and find this</p>	<p style="text-align: right;">Page 285</p> <p>1 And then the next thing I will be 2 caring about if you set the stage like you were 3 talking about, I -- I for some reason I just start 4 to investigate. I found this article. And that's 5 what I'm going to do is I read the -- the title, 6 right? That title is irrelevant, but if I do 7 this, I do scan. 8 I saw, okay, there is multiple 9 schemes. Talk about this hypothetic schemes that 10 these calculations was done for this particular 11 trimethylamine, which, again, it doesn't relate to 12 anything that ZHP is trying to do. 13 And then I, more importantly, if I 14 wrote down, right? If I recalculate, these 15 authors, again, didn't do any experiment to show 16 any evidence that what -- whatever they see they 17 actually hypothesize. 18 Actually, the -- so if I'm ZHP -- 19 like you said, right, I'm not against those. 20 Let's just follow what you set up the stage. 21 Although I don't agree those will happen. 22 Even if that's the case, if I'm ZHP, 23 I read. I won't pay attention because I won't 24 read the detail about what the, you know, the</p>

<p style="text-align: right;">Page 286</p> <p>1 Introduction will talk about because really there 2 are two major facts, right? 3 So their title has only a sole 4 substrate discussed in the whole paper in the 5 model establishment. Second, there's no evidence 6 from experiment at all to show any evidence any of 7 these theory is correct. 8 Q. Do you have any idea what the 9 purpose of the risk assessment was that ZHP was 10 supposed to do with regard to these two 11 manufacturing processes that developed 12 nitrosamines? Do you have any idea of what the 13 purpose of that risk assessment was? 14 A. Yes. From chemistry point of view, 15 they need to see every reagent they use what 16 the -- what the -- what the change will be caused. 17 If they -- if they change any condition in their 18 environment, in -- in their reaction conditions -- 19 like the reagent, the raw material -- they're 20 going -- they're going to check and follow all the 21 intermediate information, the yield and also the 22 impurities. Like they added things they have to 23 track down where they are. 24 Every solvent they use in any</p>	<p style="text-align: right;">Page 288</p> <p>1 situation, temperatures and also the 2 volume change as well. So you still 3 have -- have endless compounds to 4 consider. 5 So as I said, we have to 6 identify the -- the compound you want to 7 test or you want to control. Before that 8 really, you know, I think it's not 9 reasonable to expect people to -- to just 10 know everything about what they do. 11 BY MR. SLATER: 12 Q. That wasn't actually my question 13 about knowing everything in the world. 14 ZHP developed these processes to 15 manufacture pills that they were going to sell 16 commercially to patients to control their blood 17 pressure. 18 You understand that's why they were 19 developing these processes, right? So they could 20 sell pills that people would buy and take for 21 blood pressure control? 22 A. Yes. 23 Q. As part of the risk assessment, I 24 just want to know your opinion. Or if you don't</p>
<p style="text-align: right;">Page 287</p> <p>1 process, they have to track it down where they 2 are, how much they have there. So they're going 3 to do this kind of control for every single step 4 on their process. That's my understanding of risk 5 control. 6 Q. Was the risk assessment supposed to 7 take into consideration whether the reactions 8 could potentially create genotoxic impurities? 9 Was that supposed to be part of the risk 10 assessment as you know? 11 MR. BERNARDO: Object to the 12 question. Vague. Overly broad. 13 THE WITNESS: Genotoxic, as I 14 said, right, is such a broad term, right? 15 So you have to be specific. If you only 16 look at the reaction, let's say NDMA 17 formation or NDEA formation, there's 18 still endless infinitive number of 19 potential harmful compound out there, 20 even if you limit to that specific 21 process. 22 Because you still have 23 multiple reagent, multiple steps, and 24 multiple mixtures at every given</p>	<p style="text-align: right;">Page 289</p> <p>1 have an opinion. I need to know the scope of what 2 your -- your expertise goes to and what you think 3 you can draw opinions on. 4 Do you have enough of an 5 understanding of the purpose of the risk 6 assessment in terms of protecting against quality 7 or purity issues that could be dangerous to the 8 health of patients in terms of how extensive the 9 risk assessment was supposed to be? 10 Do you have any understanding of 11 that at all? 12 MR. BERNARDO: Object to the 13 form of the question. Asked and 14 answered. 15 THE WITNESS: Yeah, I'm here 16 as an organic chemistry -- chemist. I -- 17 I already explained my -- my 18 understanding about risk assessment from 19 the chemistry point of view of each 20 reaction, each reagent, each solvent they 21 use. 22 I also comment in my report 23 about what ZHP have known to actually 24 done according to those areas.</p>

<p style="text-align: right;">Page 290</p> <p>1 So in term of preparatory, we</p> <p>2 discuss earlier. I'm not qualified to</p> <p>3 comment on those.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Let's go to page 459 of this</p> <p>6 article, please.</p> <p>7 I want to go to the right-hand</p> <p>8 column, the bottom right. Just above the last</p> <p>9 paragraph.</p> <p>10 And you can see at the very bottom</p> <p>11 of the last paragraph on the right-hand column,</p> <p>12 there's a sentence that says --</p> <p>13 (Music)</p> <p>14 Looking at the last full paragraph</p> <p>15 in the right-hand column on page 459 of this 2010</p> <p>16 article, it says:</p> <p>17 "The nitrosation of secondary amines</p> <p>18 has already been extensively studied, and the DMA</p> <p>19 has been confirmed to be easily nitrosated into</p> <p>20 NDMA in an acidic nitrite solution."</p> <p>21 Do you see what I just read?</p> <p>22 A. I saw the sentence that you just</p> <p>23 read.</p> <p>24 Q. The nitrosation in the zinc chloride</p>	<p style="text-align: right;">Page 292</p> <p>1 DMA in their reaction.</p> <p>2 So I think we talk about this</p> <p>3 multiple times already, but this</p> <p>4 particular reaction I mention already.</p> <p>5 My opinion is very clear. It's</p> <p>6 documented --</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Okay. Let me ask you.</p> <p>9 A. -- it's not common.</p> <p>10 Q. Sorry. I didn't mean to interrupt.</p> <p>11 A. Can I finish?</p> <p>12 Q. Yeah, go ahead.</p> <p>13 A. Yeah, but it's not common, okay?</p> <p>14 And here I think you got confused or I didn't</p> <p>15 explain myself clear.</p> <p>16 It's not this reaction is not -- is</p> <p>17 not documented. It's documented. But the fact</p> <p>18 that ZHP, they don't know anywhere in their</p> <p>19 reaction they can form DMA. Therefore, they don't</p> <p>20 have a reason to test.</p> <p>21 I want to make it clear this time.</p> <p>22 Q. Okay. You agree the reaction</p> <p>23 described in this sentence was documented in the</p> <p>24 scientific literature before they developed these</p>
<p style="text-align: right;">Page 291</p> <p>1 process occurred in an acidic nitrite solution,</p> <p>2 correct?</p> <p>3 A. The quenching process, yes.</p> <p>4 Q. If ZHP had actually done research</p> <p>5 and found this article, would you agree with me</p> <p>6 that this would have been enough to place them on</p> <p>7 notice that as part of their risk assessment, they</p> <p>8 should at least test what was being manufactured</p> <p>9 with the zinc chloride process to rule out NDMA</p> <p>10 being formed?</p> <p>11 A. I disagree with that.</p> <p>12 Q. So your opinion is that they could</p> <p>13 just ignore the potential creation of NDMA, a</p> <p>14 genotoxic impurity?</p> <p>15 MR. BERNARDO: Object to the</p> <p>16 form of the question.</p> <p>17 THE WITNESS: I disagree with</p> <p>18 -- I disagree with just what you just</p> <p>19 said because this talk about what you</p> <p>20 know. There's secondary amine</p> <p>21 specifically dimethylamine and also</p> <p>22 nitric acid, right?</p> <p>23 So, but the fact is that they</p> <p>24 don't know if they have dimethylamine or</p>	<p style="text-align: right;">Page 293</p> <p>1 processes, correct?</p> <p>2 A. I agree the reaction between DMA or</p> <p>3 secondary amine, simple secondary amine like DEA,</p> <p>4 for instance, with nitrosonium ion is documented.</p> <p>5 Q. That's all I asked.</p> <p>6 A. Right. I agree.</p> <p>7 Q. Okay. And your opinion is because</p> <p>8 ZHP didn't know that there could be DMA in the</p> <p>9 process, there was no reason for them to be</p> <p>10 concerned about this nitrosation reaction.</p> <p>11 Is that what you were just telling</p> <p>12 me?</p> <p>13 A. It's almost, right? I said, yes,</p> <p>14 what you said is part of my statement. They don't</p> <p>15 know this. Therefore, they don't know NDMA</p> <p>16 formation.</p> <p>17 The other is, I also said that for</p> <p>18 the formation of nitrosonium ion is also something</p> <p>19 not that common. It's not like when you add</p> <p>20 sodium nitrite. Everybody knows there is</p> <p>21 nitrosonium ion. Sodium nitrite doesn't equal to</p> <p>22 nitrosonium ion.</p> <p>23 I never named or -- or described</p> <p>24 sodium nitrite as a nitrosative reagent. They</p>

<p style="text-align: right;">Page 294</p> <p>1 don't know this, right?</p> <p>2 So it's -- it's there. I don't say</p> <p>3 -- I don't say it's not there, right, but it's not</p> <p>4 like everybody knows that automatically.</p> <p>5 Q. If ZHP had known of the potential</p> <p>6 for DMA to be introduced into the zinc chloride</p> <p>7 process, in that case, you would agree with me</p> <p>8 that as part of their risk assessment, it would</p> <p>9 have been prudent for them to evaluate whether</p> <p>10 NDMA was being created, right?</p> <p>11 A. Well, I won't say they must know</p> <p>12 that, right? I say this particular reaction you</p> <p>13 just read me is documented. So it's there. So as</p> <p>14 people can actually learn it, but there are two</p> <p>15 parts. One part is the DMA part. They just have</p> <p>16 no idea about it, right?</p> <p>17 So the other part is also not</p> <p>18 common. It's not like everybody learn general</p> <p>19 chemistry, go through graduate school. They all</p> <p>20 know nitrosonium ion equal sodium nitrite. They</p> <p>21 are not. You use sodium nitrite for multiple</p> <p>22 reaction as a quenching reagent. I personally</p> <p>23 never used it, but they are used, right? So I</p> <p>24 knew that, right?</p> <p style="text-align: right;">Page 295</p>	<p style="text-align: right;">Page 296</p> <p>1 THE WITNESS: Can you please</p> <p>2 chop your question little shorter?</p> <p>3 Because I, you know, I'm...</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Number one, the chemists had to know</p> <p>6 that they were creating an acidic nitrite solution</p> <p>7 at the quenching phase, right?</p> <p>8 A. Yes, they know that.</p> <p>9 Q. Number two, they knew they were</p> <p>10 using DMF and introducing that to the zinc</p> <p>11 chloride process, correct?</p> <p>12 A. Yes, they knew they used DMF.</p> <p>13 Q. If they knew that the DMF could</p> <p>14 introduce DMA to the zinc chloride process, either</p> <p>15 as an impurity or as a degradation product, then</p> <p>16 under those circumstances, they would have been</p> <p>17 required to take the prudent step of testing to</p> <p>18 see if NDMA was being formed, correct?</p> <p>19 MR. BERNARDO: Object. Object</p> <p>20 to the form of the question. Vague.</p> <p>21 Outside the scope of his expertise.</p> <p>22 THE WITNESS: Yeah. Well, for</p> <p>23 the required part I cannot comment too</p> <p>24 much, but I'll say, right? So my --</p> <p style="text-align: right;">Page 297</p>
<p>1 So it is not -- we cannot draw a</p> <p>2 simple equation and say everybody knows that.</p> <p>3 Yeah, I recall, you know, some of the expert on</p> <p>4 the plaintiff side said that. I really cannot</p> <p>5 agree with that.</p> <p>6 Q. You would agree that the chemists at</p> <p>7 ZHP should have known that there was going to be</p> <p>8 in acidic nitrite solution at the quenching phase,</p> <p>9 right?</p> <p>10 A. Yes, because that's what they used.</p> <p>11 Q. And this article says that DMA has</p> <p>12 been confirmed to be easily nitrosated in NDMA in</p> <p>13 an acidic nitrite solution.</p> <p>14 So if ZHP had been aware of the</p> <p>15 potential for DMA to be introduced to the zinc</p> <p>16 chloride process, either as an impurity of the DMF</p> <p>17 or as a degradation product of DMF, under those</p> <p>18 circumstances, they would have been on notice as</p> <p>19 part of their risk assessment of the need to test</p> <p>20 to determine if NDMA was being formed.</p> <p>21 Do I now understand the difference?</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. The</p> <p>24 characterization of his testimony.</p>	<p>1 my -- my opinion state clearly. This</p> <p>2 reaction is a known reaction. It's</p> <p>3 documented. But it's not common, right?</p> <p>4 So both of the substrates are</p> <p>5 required. I said even those are there,</p> <p>6 they are not very common people will</p> <p>7 know. Because sodium nitrite you cannot</p> <p>8 just draw an equation and say it equals</p> <p>9 nitrosonium ion.</p> <p>10 And for the secondary amine,</p> <p>11 they don't know, right? So if you say,</p> <p>12 oh, they already know they have a</p> <p>13 secondary amine, then they automatically</p> <p>14 will know this reaction will take place.</p> <p>15 That's my opinion, right?</p> <p>16 So I said, yes, it's</p> <p>17 documented. This reaction is documented.</p> <p>18 People knew this. I never say this never</p> <p>19 published or nobody knows. There are</p> <p>20 publications on this particular reaction</p> <p>21 when you have the secondary amine and</p> <p>22 your nitrosonium ion. But nitrosonium</p> <p>23 ion, you need to figure out that you have</p> <p>24 nitrosonium ion.</p>

<p style="text-align: right;">Page 298</p> <p>1 And when you have those two 2 together, you still need to have some 3 knowledge about this reaction there to be 4 aware there's reaction take place. 5 Could there still be multiple 6 stage? A chemist at ZHP has to kind of 7 get together at the same time with the 8 people assumption that they know there 9 DMF contains or degrade to form DMA, 10 which we talked about so many times that 11 they don't know. 12 BY MR. SLATER: 13 Q. The whole thought process you just 14 walked through, ZHP never went through that 15 thought process because they never evaluated any 16 of this literature, any of these questions, right? 17 MR. BERNARDO: Object to the 18 form of the question. Vague. 19 BY MR. SLATER: 20 Q. Nothing you've seen, right? 21 A. Well, I'm -- I'm here -- 22 Q. Doctor, could you just answer my 23 question, please? 24 ZHP never even considered what you</p>	<p style="text-align: right;">Page 300</p> <p>1 case, I have zero -- 2 Q. I'm sorry. That's not what I asked 3 you, and I don't have unlimited time. 4 A. Right. So you -- you ask me -- 5 Q. What you saw in the records and the 6 documents you read -- 7 A. Uh-huh. 8 Q. -- you saw in the materials -- new 9 question. 10 In the materials you reviewed, you 11 saw no indication that anybody at ZHP thought at 12 all about any of the things you talked about in 13 your prior answer in terms of analyzing the 14 literature because they never went that far to 15 actually even look at the literature on this 16 question, right? 17 MR. BERNARDO: Dr. Xue, I know 18 it's late. Just listen to what 19 Mr. Slater is asking. He's simply asking 20 if you've seen anything in the documents 21 you looked at. 22 THE WITNESS: I didn't see 23 any documents directly showing that. 24 MR. SLATER: I'm getting --</p>
<p style="text-align: right;">Page 299</p> <p>1 just went through. They never went through a 2 thought process of whether or not there was an 3 issue with any of the things you just went 4 through. 5 It's just something they never 6 thought about, correct? 7 MR. BERNARDO: Object to the 8 form of the question. Argumentative. 9 THE WITNESS: Yeah, I cannot 10 speculate other people's thought. I 11 do -- 12 BY MR. SLATER: 13 Q. Did you see anything indicating that 14 they thought about any of these things? 15 A. What specific things you talk? 16 Q. What we just talked through. That 17 whole description you gave of the whole thought 18 process you'd have to go through in evaluating the 19 literature. 20 You've seen nothing indicating that 21 anyone at ZHP thought about any of those things, 22 right? 23 A. Well, I'll put it this way. If you 24 ask me in October before I'm involved in this</p>	<p style="text-align: right;">Page 301</p> <p>1 this is probably a good time to take a 2 break. 3 MR. BERNARDO: Sure. 4 THE VIDEOGRAPHER: Time right 5 now is 4:21 p.m. We're off the record. 6 (Recess.) 7 THE VIDEOGRAPHER: Time right 8 now is 4:36 p.m. We're back on record. 9 MR. SLATER: Let's put up the 10 deviation investigation report again, 11 Exhibit -- which was Exhibit 5. We'll go 12 to page 155, please. 13 Just one second before I do 14 this. 15 Sorry about that. 16 BY MR. SLATER: 17 Q. Looking now at page 154 of this 18 deviation investigation report, you can see the 19 middle of the page: 20 "Test Result of Triethylamine 21 Hydrochloride Samples by Huahai." 22 You see that? 23 A. So you talk about the page 155. 24 Q. I said 154.</p>

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1 A. Oh, I'm sorry. 154.
2 You said there is what?
3 Q. On page 154 in the middle of the
4 page, you'll see it says number 4?
5 A. Right.
6 Q. In the middle of the page, it says
7 number 4) "Test Result of Triethylamine
8 Hydrochloride Samples by Huahai."
9 You see that?
10 A. Yes. But can you please make it
11 bigger? Thank you.
12 Q. Okay.
13 A. That's great.
14 Q. It then says analytical -- well,
15 rephrase.
16 It says:
17 "Analytical method for DEA and DMA
18 and Triethylamine Hydrochloride was developed by
19 Huahai, and the Triethylamine Hydrochloride (from
20 Kente Catalytic materials Co., Ltd) in stock was
21 analyzed. The DMA and DEA results obtained was in
22 Table 4-30 as follows."
23 You see that table below?
24 A. You talk about Table 4-30.

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1 Q. You see it right there in front of
2 you?
3 A. Yeah, yeah. Okay. Yeah.
4 Q. First of all, triethylamine
5 hydrochloride, was that used in the TEA with
6 sodium nitrite quenching process?
7 A. I'm sorry. Your -- your voice was
8 chopped off just now. I just heard the word
9 "process" just now.
10 Q. Was triethylamine hydrochloride used
11 in the TEA with sodium nitrite quenching process?
12 A. Yes. Yes.
13 Q. That's what we've been referring to
14 as triethylamine, right?
15 A. Yes.
16 Q. And you can see that they tested for
17 DEA and DMA and they found DEA at 106.3 parts per
18 million.
19 You see that?
20 A. I saw that from the table that you
21 show.
22 Q. Let's go to the next page. Well,
23 actually, let's stop there for a second. I didn't
24 mean to jump that quickly.

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1 So this is -- rephrase.
2 This is ZHP confirming that the
3 triethylamine hydrochloride they used in that
4 process contained as an impurity DEA, correct?
5 MR. BERNARDO: Object to the
6 form of the question. Vague.
7 THE WITNESS: So what I can
8 read from this table is for this batch
9 number -- I don't need to read the
10 number -- I think they tested for DMA and
11 DEA.
12 Can we know what LOD -- LOD
13 for limit?
14 BY MR. SLATER:
15 Q. Level of detection.
16 A. Level of detection. Okay.
17 So I can read that for DMA for
18 whatever method they are using to detect this,
19 it's already below that. So I think the -- the
20 level set for the detection was 45 ppm. And then
21 with DEA, their detect result for this batch was
22 actually 106.3 ppm. That's it.
23 Q. You would agree with me that ZHP was
24 purchasing triethylamine hydrochloride to use in

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1 the manufacturing process for valsartan.
2 You would agree that under those
3 circumstances, ZHP should have known of the
4 potential impurities in that product that they
5 were going to include in their process?
6 MR. BERNARDO: Object to form
7 of the question. Vague.
8 BY MR. SLATER:
9 Q. Or were they allowed to just be
10 ignorant of the impurities that might be
11 introduced into the process and not worry about
12 it?
13 MR. BERNARDO: Object to the
14 form of the question. Vague.
15 Argumentative.
16 THE WITNESS: I disagree with
17 what you just said.
18 BY MR. SLATER:
19 Q. Okay. You disagree. That's fine.
20 Let me ask the question differently.
21 Did ZHP need to know if there was a
22 substance it was going to introduce into its
23 manufacturing process, if that substance had
24 impurities that could be introduced into the

<p style="text-align: right;">Page 306</p> <p>1 process? Did they have to know whether or not 2 that could happen?</p> <p>3 MR. BERNARDO: Object to the 4 form of the question. Vague.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Yes, no, or you have no opinion. 7 A. I don't think I'm clear about what 8 you asking. You are saying -- 9 Q. I'll be even more clear. 10 ZHP was using triethylamine 11 hydrochloride to manufacture valsartan, right? 12 A. That's correct. 13 Q. As shown here on this deviation 14 investigation report from ZHP, triethylamine 15 hydrochloride has DEA as an impurity in the 16 commercially sold form of that substance. 17 You see that? That's what this 18 document is showing, right? 19 MR. BERNARDO: Object to the 20 form of the question. Vague. 21 Characterization of the document. 22 THE WITNESS: Well, as the 23 document was -- was looking backward from 24 2018, right? So they knew already at</p>	<p style="text-align: right;">Page 308</p> <p>1 here in their report is that, okay, so 2 the DMA possibly not. If there is, it's 3 definitely below their -- their -- their 4 LOD. And they did find DEA in the -- 5 they come, you know, in the triethylamine 6 sample, the particular batch that they 7 use for this, right? 8 So I think that this is very 9 logic, right? So I don't see if there 10 are any questions because we -- they did 11 what they did. 12 BY MR. SLATER: 13 Q. You literally just told me what the 14 document shows and that is not -- I didn't ask you 15 to explain to me what the document shows. We 16 already went through that. So I'm going to try 17 the question again. 18 Should ZHP -- well, first of all, 19 let me ask you a foundational question. 20 A. Sure. 21 Q. You agree that it's more likely than 22 not that the triethylamine hydrochloride that ZHP 23 used in the TEA with sodium nitrite quenching 24 process contained DEA as an impurity when they</p>
<p style="text-align: right;">Page 307</p> <p>1 this moment when they actually do this 2 analysis where in their -- in their 3 process DMA was formed. And then as you 4 read in the last section there, they also 5 have emphasize the reason why it can 6 happen, right? 7 So they have the dimethylamine 8 as a reactant. They said somewhere on 9 the process there might be dimethylamine 10 there. They also there, the other part, 11 nitrosonium ion somewhere on this process 12 you can form. 13 They say when these two 14 together, when they meet in the reaction 15 vessel, they can possibly form. That's 16 what they actually hypothesize. 17 Here is what they actually 18 show. After they know, okay? In my 19 process in PA with quenching, I saw NDEA. 20 And then I start to track it back to see, 21 okay, what -- whether there's actually, 22 you know, they're basically hunting down 23 where the DEA actually come from. 24 So what they found and report</p>	<p style="text-align: right;">Page 309</p> <p>1 actually were manufacturing valsartan. 2 Do you agree? Yes, no, or you have 3 no opinion. 4 A. I cannot agree because we have to 5 set the -- set the scope, right? 6 Q. You said, no, you don't agree. 7 Okay. 8 A. So this -- this table tells us for 9 this particular batch -- 10 Q. I'm not asking about this table, 11 Doctor, and I don't have unlimited time. So I 12 just need you to answer my question. 13 I'm asking a very straightforward 14 question. Look at me maybe, not at the document 15 maybe we will -- because you're focused on the 16 document. I'm trying to ask you a question not 17 about the document now. Okay? 18 I'm asking about ZHP when they 19 developed and used the manufacturing process. 20 Okay? 21 A. Uh-huh. Yes. 22 Q. That's the time frame. 23 During that time, in your opinion, 24 did the triethylamine that was utilized contain</p>

<p style="text-align: right;">Page 310</p> <p>1 DEA as an impurity already before it was inserted 2 into the manufacturing process? 3 Either your opinion is yes, it was 4 there, no, it wasn't there, or "I don't have an 5 opinion." That's what I'm asking you. 6 A. So you ask my opinion whether I 7 believe the TEA catalyst they use in their TEA 8 process with quenching contained an impurity DEA, 9 right? So, but you ask me this question today. 10 Q. Why don't you just answer the 11 question, please, instead of giving me a speech. 12 A. I really can't because you ask me 13 today. I, of course, know now based on the data 14 they look backward. They showed, yes, there is, 15 but that doesn't really solve the puzzle, right? 16 So they don't know before and they are not -- they 17 are not looking at that time when they develop 18 for -- 19 Q. Doctor, I'm sorry to interrupt you, 20 but I didn't ask you about what they were looking 21 for. I asked if you had an opinion as to whether 22 it was there. 23 You just told me, in your opinion, 24 yes, there was DEA in the triethylamine.</p>	<p style="text-align: right;">Page 312</p> <p>1 less than the level of detection 45 parts per 2 million." 3 We just looked at that, correct? 4 That's what we just looked at on the prior page? 5 That's what I just showed you. 6 A. Yes. 7 Q. Okay. The next sentence says: 8 "However, DMA was detected in one 9 batch of Triethylamine Provided by Zhejiang Jianye 10 Chemicals Company Limited. The result is in Table 11 4-31 as follows." 12 So you can see they have 13 Triethylamine Test Results down below from a 14 different manufacturer. 15 Do you see that? 16 A. You talk about Table 4 dash? 17 Q. Table 4-31. It's literally there 18 right there on the screen. 19 A. Okay. 20 Q. Do you see that they tested that 21 triethylamine that they purchased from this 22 manufacturer, Zhejiang Jianye Chemicals Company 23 Limited, and they gave the results in that table. 24 You see the results in front of you,</p>
<p style="text-align: right;">Page 311</p> <p>1 A. I -- 2 Q. I didn't ask you about their 3 research. I asked you one question. I don't have 4 unlimited time. So I need you to just answer the 5 questions I'm asking, please. 6 A. My answer is, when I look at now, 7 yes, they have the TEA in there. But this is 8 looking backward when they actually figure out. 9 They don't know whether they have it. My -- if 10 you want me a yes or no -- 11 Q. I literally didn't ask you if they 12 knew it was there. I asked what your opinion was 13 as to whether it was there. I don't understand 14 why you persist in giving me speeches about things 15 I'm not asking you, sir. 16 Let's go to the next page, page 155. 17 If you go to the middle of the page. 18 Scroll down so we can get the whole middle. Right 19 there, yeah. 20 Looking at the middle of page 155 of 21 this deviation investigation report from ZHP, it 22 says: 23 "The results indicate the presence 24 of DEA in Triethylamine Hydrochloride, and DMA was</p>	<p style="text-align: right;">Page 313</p> <p>1 correct? 2 A. I do see the table saying for three 3 batches this time, right? 4 Q. You can see for one batch they 5 actually had 8.2 parts per million of DMA. 6 You see that? 7 A. Sorry. What was the LOD for this 8 one? 9 Q. Level of detection. I don't know. 10 I'm sorry. 11 Can you just answer the question, 12 please? 13 My question again is: If you look 14 at the table, it shows the results for testing for 15 DMA and DEA as impurities of the triethylamine 16 from this manufacturer. 17 You see that in front of you, 18 correct? 19 A. I do see that number. But can I 20 ask? Because the last LOD was 45. I just 21 curious. Because every experiment has errors, 22 right? So -- 23 Q. Don't know. I only know what the 24 report says. This is all I know is what's right</p>

<p style="text-align: right;">Page 314</p> <p>1 in front of you.</p> <p>2 A. Yeah, I can read those numbers. I'm</p> <p>3 with you on those numbers.</p> <p>4 Q. So it shows that -- it shows in the</p> <p>5 first batch, which is the last three digits are</p> <p>6 013, it had DMA of 8.2 parts per million and DEA</p> <p>7 of 85.3 parts per million.</p> <p>8 That's documented, right?</p> <p>9 A. That is the numbers are correct,</p> <p>10 but, again, I want to -- if as a scientist --</p> <p>11 Q. I'm just asking you if you can see</p> <p>12 the numbers in front of you.</p> <p>13 Is that what the numbers say?</p> <p>14 A. Yeah, I can see the numbers.</p> <p>15 Q. The second batch 014, it said that</p> <p>16 no DMA was detected. That's what ND says, not</p> <p>17 detected. And it had DEA of 28.6 parts per</p> <p>18 million.</p> <p>19 Do you see that?</p> <p>20 A. I see the two as you read.</p> <p>21 Q. And the third batch 015, for DMA it</p> <p>22 says ND, not detected, and for DEA 26.1 parts per</p> <p>23 million.</p> <p>24 You see that?</p>	<p style="text-align: right;">Page 316</p> <p>1 A. Okay.</p> <p>2 Q. -- do you see any indication during</p> <p>3 that time period that anyone at ZHP realized that</p> <p>4 DEA was an impurity in the triethylamine that they</p> <p>5 were using? Yes or no.</p> <p>6 A. I cannot comment on that. I</p> <p>7 don't -- I don't -- I don't read anything about</p> <p>8 it. I didn't see any evidence about that.</p> <p>9 Q. You would agree with me that it was</p> <p>10 well-documented in the literature for somebody who</p> <p>11 was a chemist who actually was doing a rigorous</p> <p>12 scientific literature search as part of a risk</p> <p>13 assessment for a drug manufacturing process, if</p> <p>14 they looked, they would have been able to find the</p> <p>15 literature saying that under the conditions of</p> <p>16 that process, the sodium nitrite and the processes</p> <p>17 that were happening could potentially nitrosate</p> <p>18 the DEA and create NDMA.</p> <p>19 You would agree that that</p> <p>20 information was out there if they had looked,</p> <p>21 correct?</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. Compound.</p> <p>24 Argumentative.</p>
<p style="text-align: right;">Page 315</p> <p>1 A. Yes.</p> <p>2 Q. Now, my question is this: Based on</p> <p>3 the fact that there was DEA impurity in the</p> <p>4 triethylamine -- well, let me ask you this, first</p> <p>5 of all.</p> <p>6 Did you see any indication that</p> <p>7 anyone at ZHP actually noticed that there was DEA</p> <p>8 as an impurity of the triethylamine they used in</p> <p>9 the TEA with sodium nitrite process?</p> <p>10 My question is: Of everything you</p> <p>11 looked at, did anybody at ZHP ever realize that?</p> <p>12 That's my first question. Did you</p> <p>13 see anything to that effect?</p> <p>14 A. So you're asking --</p> <p>15 Q. That's the question.</p> <p>16 A. You're asking the data that we show</p> <p>17 here in this table --</p> <p>18 Q. No, I'm not asking about this data.</p> <p>19 I'm asking: Did anybody from ZHP</p> <p>20 back when they were manufacturing the valsartan</p> <p>21 with the sodium nitrite with TEA -- rephrase.</p> <p>22 Back when ZHP was developing and</p> <p>23 using the TEA with sodium nitrite quenching</p> <p>24 process --</p>	<p style="text-align: right;">Page 317</p> <p>1 Go ahead.</p> <p>2 THE WITNESS: I disagree.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. Fine. You disagree.</p> <p>5 Do you disagree because it's your</p> <p>6 opinion that unless there's an article that</p> <p>7 replicates the exact conditions of the process</p> <p>8 that they intended to use, they don't have to</p> <p>9 think about it as a potential issue?</p> <p>10 A. No, I never said that.</p> <p>11 I use the general practice of -- of</p> <p>12 science, right? So every science has a scope,</p> <p>13 right? You cannot just artificially expand your</p> <p>14 scope of your understanding by saying this or that</p> <p>15 is for sure, everybody knows.</p> <p>16 I -- my approach is rely on the</p> <p>17 reference and what's available. So I did my</p> <p>18 search. I found for -- for the secondary amine</p> <p>19 reaction, if you know there's a secondary amine,</p> <p>20 it's documented. But it's not as common as the</p> <p>21 expert of the plaintiffs claim.</p> <p>22 And for the tertiary amine, it's --</p> <p>23 it's much more complicated. I didn't know my</p> <p>24 personally. I never teach. I never really do any</p>

<p style="text-align: right;">Page 318</p> <p>1 research before I'm involved in this case.</p> <p>2 By reading more recent papers</p> <p>3 discuss about this, I have no clue about this</p> <p>4 reaction. So that's how I form my opinion.</p> <p>5 I mean, these batches as you showing</p> <p>6 here, they shows, yes, these batch when they look</p> <p>7 back, they did find DEAs in their multiple</p> <p>8 batches.</p> <p>9 I just don't see why this will help</p> <p>10 them to actually figure out because this</p> <p>11 everything they did here -- they did here is</p> <p>12 backward. We now sitting 2023 talking about this</p> <p>13 happening 2003. 2013. I'm sorry.</p> <p>14 Q. DEA is a secondary amine, right?</p> <p>15 A. DEA is dimethylamine. It is a</p> <p>16 secondary amine.</p> <p>17 Q. And it was well-documented in the</p> <p>18 literature that a secondary amine could be</p> <p>19 nitrosated, correct?</p> <p>20 MR. BERNARDO: Object to the</p> <p>21 form of the question. Vague.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. During the entire time they</p> <p>24 developed and used these processes, it was</p>	<p style="text-align: right;">Page 320</p> <p>1 MR. BERNARDO: Wait, Dr. Xue.</p> <p>2 Object to the form of the</p> <p>3 question. Asked and answered. Assumes</p> <p>4 facts. Vague. Compound.</p> <p>5 Go on.</p> <p>6 THE WITNESS: That's not</p> <p>7 correct.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. Okay. What this --</p> <p>10 A. You have a lot of hypothetical</p> <p>11 situation added in there. I cannot really answer</p> <p>12 question with so many hypothesis. I already state</p> <p>13 my opinion clearly about these two situations.</p> <p>14 MR. SLATER: Okay. Let's --</p> <p>15 let's look at this, too. Just -- let's</p> <p>16 go to the next document.</p> <p>17 (Document marked for</p> <p>18 identification as Xue Exhibit 13.)</p> <p>19 THE WITNESS: Now is this 14,</p> <p>20 12 or 13?</p> <p>21 MR. SLATER: What number is</p> <p>22 this? 13.</p> <p>23 THE WITNESS: Hold on. I'm</p> <p>24 still loading. I only see 12.</p>
<p style="text-align: right;">Page 319</p> <p>1 well-documented in the literature that a secondary</p> <p>2 amine could be nitrosated, correct?</p> <p>3 A. As I said --</p> <p>4 Q. You said that, right?</p> <p>5 A. I said that secondary amine can be</p> <p>6 nitrosated. It's documented, right, multiple</p> <p>7 times. But I said --</p> <p>8 Q. That's all I asked you, Doctor. I</p> <p>9 didn't ask for another speech. I asked if it was</p> <p>10 well-documented. You agreed. We're fine.</p> <p>11 A. No, I said it's documented. I never</p> <p>12 said it's well-documented.</p> <p>13 Q. Okay. It's documented.</p> <p>14 A. Thank you.</p> <p>15 Q. If ZHP had actually done a</p> <p>16 literature search, found the literature</p> <p>17 documenting that a secondary amine could be</p> <p>18 nitrosated, and they had then said, well, since</p> <p>19 this could potentially happen in general, let's</p> <p>20 test for NDMA and they used mass spectrometry,</p> <p>21 they would have been able to find the NDMA.</p> <p>22 Is that correct? Yes, no, or you</p> <p>23 have no opinion?</p> <p>24 A. That --</p>	<p style="text-align: right;">Page 321</p> <p>1 BY MR. SLATER:</p> <p>2 Q. It's only one page. It's the page</p> <p>3 on the screen. That's the whole exhibit.</p> <p>4 A. Yeah, I can see the page on the</p> <p>5 screen.</p> <p>6 Q. All right. Just what we did is, we</p> <p>7 found on the Internet this Certificate of Analysis</p> <p>8 from the same company that was discussed in that</p> <p>9 Table 4.31 we just went through, and you can see</p> <p>10 it's dated November 25, 2012 just above the table.</p> <p>11 And you can see that it shows the</p> <p>12 triethylamine analysis showed that there was</p> <p>13 diethylamine in that product.</p> <p>14 Do you see that?</p> <p>15 A. So I never see this document before.</p> <p>16 Q. Do you see that it shows that there</p> <p>17 was diethylamine noted in the Certificate of</p> <p>18 Analysis for the triethylamine sold by this</p> <p>19 manufacturer?</p> <p>20 I'm literally just asking you do you</p> <p>21 see that it documented the presence of</p> <p>22 diethylamine.</p> <p>23 A. I saw this. So there's entry.</p> <p>24 Because I have to -- because I never seen it</p>

<p style="text-align: right;">Page 322</p> <p>1 before, I need to understand what this document 2 is, right? I think that that's reasonable, right? 3 So -- so there is an entry talk 4 about diethylamine. 5 So what "WT" stand for? 6 Q. I'm guessing percentage by weight, 7 but you're the scientist. I'm the guy who failed 8 those science classes. 9 A. Well, yeah. So I think that that's 10 a number that I need to know what -- what that 11 means. 12 Q. Okay. 13 A. I think that's a good guess, but I 14 really don't know what that is. 15 Q. Okay. Does that prevent you from 16 saying that you can see that -- 17 A. No. No. 18 Q. -- triethylamine they found that 19 there was diethylamine in the triethylamine? 20 It's there, right? You see it on 21 the page, right? 22 A. Well, because -- 23 Q. Doctor, do you see it on the page? 24 I'm not asking for an explanation</p>	<p style="text-align: right;">Page 324</p> <p>1 you to give you any Certificate of Analysis that 2 they had for the DMF or the triethylamine that was 3 used by ZHP? 4 A. Well, early on I said -- 5 Q. Doctor, it's a simple question. 6 Did you ask for a Certificate of 7 Analysis from the lawyers or not? 8 A. I didn't -- I didn't ask for those. 9 Q. All right. Did you see any? 10 A. Sorry. You're -- you're freezing 11 for a second. 12 Q. Did you see any? 13 A. What? What? Any of what? 14 Q. Did you see any Certificate of 15 Analysis for the DMF or triethylamine used by ZHP? 16 Yes or no. 17 A. I don't remember seeing any. 18 Q. Okay. Take that down. 19 Now what we're going to do is, we're 20 going to go to some pages within the DMF, the drug 21 master file that was filed with the FDA, and it's 22 the section on impurities. The module on 23 impurities. 24 And we're going to go to page --</p>
<p style="text-align: right;">Page 323</p> <p>1 for all the reasons that you want to tell me it 2 doesn't matter. It's a simple question. So I'll 3 try it cleanly. 4 On this Certificate of Analysis 5 dated November 25, 2012, for the chemical company 6 that was discussed in the deviation investigation 7 report in Table 4.31, you can see that it 8 documents the presence of diethylamine. 9 You see that, right? 10 MR. BERNARDO: Objection. 11 Form. 12 THE WITNESS: I see 13 diethylamine there. I'm sorry. 14 BY MR. SLATER: 15 Q. Okay. Did you ever ask anybody to 16 give you any Certificate of Analysis from any of 17 the suppliers or manufacturers for the DMF or 18 triethylamine that was used in the manufacturing 19 processes for valsartan? 20 Did you ask for those documents? 21 That's all I'm asking you. 22 A. Can you repeat again? Because your 23 sentence very long. I got lost in the middle. 24 Q. Did you ask the lawyers who hired</p>	<p style="text-align: right;">Page 325</p> <p>1 A. Hold on. We talk about a new 2 exhibit -- exhibit like 14? 3 Q. We're going to go to page 100 and -- 4 A. I'm not seeing that yet in my 5 folder. 6 Q. It's just not there yet, Doctor. 7 A. Okay. I'm sorry. 8 Q. Chris is doing it right now. 9 A. Thank you for reminding me. 10 Q. No problem. 11 Let's go to page 147 of 172 first. 12 A. Please give me a second because I'm 13 still refreshing. 14 Q. It's okay. I'm just letting him 15 know where he's going. No problem. 16 (Document marked for 17 identification as Xue Exhibit 14.) 18 BY MR. SLATER: 19 Q. I'm looking at page 147 of 172. It 20 says "Discussion about Genotoxicity." 21 Do you see that? 22 A. Hold on. Give me a second. I'm 23 still loading and trying to open this. 24 You said 147?</p>

<p style="text-align: right;">Page 326</p> <p>1 Q. It's on the screen, Doctor.</p> <p>2 A. Yeah, yeah. Because can you --</p> <p>3 MR. SLATER: Help me out,</p> <p>4 Rich, please.</p> <p>5 MR. BERNARDO: He's entitled</p> <p>6 to take a look at the document, not the</p> <p>7 page that you have on the screen, Adam.</p> <p>8 MR. SLATER: Okay. Well,</p> <p>9 that's okay. We're going to have to</p> <p>10 start talking about time issues if we get</p> <p>11 into them because this has been very,</p> <p>12 very difficult.</p> <p>13 THE WITNESS: Yes, I can see</p> <p>14 this page now.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Great.</p> <p>17 This is the section with a</p> <p>18 "Discussion about Genotoxicity."</p> <p>19 Let's now go to the next page, 148</p> <p>20 of 172. It says "Discussion on Impurities" at the</p> <p>21 top of the page. And then it has -- it says</p> <p>22 "Organic impurities."</p> <p>23 "All the potential organic</p> <p>24 impurities are demonstrated in Valsartan listed as</p>	<p style="text-align: right;">Page 328</p> <p>1 Q. It says in part that there's no high</p> <p>2 potency genotoxic group, such as aflatoxin-like-,</p> <p>3 N-nitroso-, and azoxy-compound in impurities for</p> <p>4 the zinc chloride valsartan.</p> <p>5 Do you see that?</p> <p>6 MR. BERNARDO: Object to the</p> <p>7 form of the question and the</p> <p>8 characterization of what the document</p> <p>9 says.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. You see what I just read, right?</p> <p>12 A. I saw what you just read.</p> <p>13 Q. Okay. That was an untrue statement</p> <p>14 because there was actually NDMA in the valsartan</p> <p>15 manufactured with the zinc chloride process,</p> <p>16 right?</p> <p>17 MR. BERNARDO: Object to the</p> <p>18 form of the question.</p> <p>19 THE WITNESS: I need to read</p> <p>20 the -- this table a little bit because I</p> <p>21 don't remember seeing this.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. Doctor, it's a very simple question.</p> <p>24 When they -- when ZHP represented</p>
<p style="text-align: right;">Page 327</p> <p>1 follows."</p> <p>2 Do you see that?</p> <p>3 A. Yes. At the table, right?</p> <p>4 Q. Okay. And then let's go to the</p> <p>5 bottom of the table to the language there. And in</p> <p>6 the last paragraph, it says:</p> <p>7 "Regarding the impurity D through J</p> <p>8 and hydrolysis product, there is not any high</p> <p>9 potency genotoxic group, such as, aflatoxin-like-,</p> <p>10 N-nitroso-, and azoxy-compound has been included</p> <p>11 in these impurities. And these impurities are</p> <p>12 demonstrated absence in the drug substance and</p> <p>13 controlled within the any unknown impurity of NMT</p> <p>14 0.10% in the final product. These impurities are</p> <p>15 no genotoxic risk in Valsartan."</p> <p>16 Do you see what I just read?</p> <p>17 A. Sorry. There's airplane noise. Can</p> <p>18 you guys hear the noise?</p> <p>19 Q. Do you see the last paragraph on the</p> <p>20 page I just read?</p> <p>21 A. I do see the last paragraph, but I</p> <p>22 didn't quite follow your -- your -- your reading</p> <p>23 because the noise outside. I can read that</p> <p>24 paragraph myself, though.</p>	<p style="text-align: right;">Page 329</p> <p>1 that there were no N-nitroso-compounds, it was --</p> <p>2 that was not accurate because there was NDMA in</p> <p>3 the valsartan produced with the zinc chloride</p> <p>4 process, correct?</p> <p>5 MR. BERNARDO: Object to the</p> <p>6 form of the question and how you just</p> <p>7 mischaracterized the document. And he</p> <p>8 asked to read it to see what the other</p> <p>9 reference was referring to. So give him</p> <p>10 a minute to see that.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Take a look.</p> <p>13 A. (Reviews document.)</p> <p>14 So this document is very big. I</p> <p>15 recall when I first load the document, there's</p> <p>16 some structures. I want to see the structure of</p> <p>17 the drugs. Are they anywhere in the document?</p> <p>18 Q. Doctor, I asked you a specific</p> <p>19 question.</p> <p>20 Are you now looking to find out if</p> <p>21 they disclosed the presence of NDMA? I mean --</p> <p>22 A. No, no, no.</p> <p>23 Q. -- a different copy?</p> <p>24 A. I'm asking because they talk about</p>

<p style="text-align: right;">Page 330</p> <p>1 this structure G, H, and all the --</p> <p>2 Q. It's right above. It's on the same</p> <p>3 page directly above the language. It's that table</p> <p>4 right above it.</p> <p>5 MR. SLATER: Scroll down a</p> <p>6 little so he can see it.</p> <p>7 THE WITNESS: Yeah, I -- I --</p> <p>8 MR. SLATER: Chris, please.</p> <p>9 THE WITNESS: What the page</p> <p>10 number again for this? I went back to</p> <p>11 the first page. I need to go back.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. Right there in front of you on the</p> <p>14 screen. 148. That's literally the table that's</p> <p>15 being referred to.</p> <p>16 A. 148. I'm -- okay. So I'm on 148.</p> <p>17 So the reading of this second</p> <p>18 paragraph that you just read to me regarding to</p> <p>19 the impurity D through J, N is hydrolysis</p> <p>20 products, okay? Those -- those compounds.</p> <p>21 All right. So what they describe is</p> <p>22 these compound structure doesn't actually has any</p> <p>23 of those listed functionalities including nitroso</p> <p>24 was in the structure, right?</p>	<p style="text-align: right;">Page 332</p> <p>1 time before 2018 testing?</p> <p>2 A. Before 2018, I didn't see any</p> <p>3 evidence. Because they -- as my opinion, they</p> <p>4 don't have any clue and they don't have any reason</p> <p>5 to test. But after, yes, we believe especially at</p> <p>6 the end of the day, they have the root cause</p> <p>7 analysis to see what is the possible reason. They</p> <p>8 raise hypothesis.</p> <p>9 Q. Okay. We're going to take that</p> <p>10 down.</p> <p>11 You talked in your report about the</p> <p>12 July 27, 2007 e-mail sent by Jinsheng Lin to Min</p> <p>13 Li and others.</p> <p>14 Do you recall writing about that in</p> <p>15 your report?</p> <p>16 A. I -- I do.</p> <p>17 Q. All right. Did you read Min Li's</p> <p>18 testimony in his deposition where he talked about</p> <p>19 what the e-mail said?</p> <p>20 A. Well, I -- I read depositions from</p> <p>21 multiple people. I definitely read Min Li's</p> <p>22 deposition, but I don't know whether I read every</p> <p>23 single line of that.</p> <p>24 By the way, are you -- are you going</p>
<p style="text-align: right;">Page 331</p> <p>1 So, and, therefore, they are not --</p> <p>2 they are not qualified as high, you know, toxic</p> <p>3 compound because they don't have any of those</p> <p>4 three structures -- groups. And because of that,</p> <p>5 they are saying they are not quantified --</p> <p>6 qualified as high potency genotoxic groups.</p> <p>7 And then they say these impurities</p> <p>8 are -- are -- their -- their presence is actually</p> <p>9 within the controlled NMT -- I don't know what NMT</p> <p>10 stands for -- but within the controlled relation.</p> <p>11 Therefore, they say there's no genotoxic risk.</p> <p>12 I don't -- I don't see if there's</p> <p>13 any problem because they -- these structures, as I</p> <p>14 saw on the first page of the document, they have</p> <p>15 none of this containing these listed</p> <p>16 functionalities. Therefore, they are not high</p> <p>17 risk and presumably the non-high risk compound has</p> <p>18 a limit of .10 percent.</p> <p>19 Now, they are all okay. That's what</p> <p>20 they talk about here.</p> <p>21 Q. All right. Did they -- did ZHP do</p> <p>22 any testing for NDMA or NDEA, or any other</p> <p>23 nitrosamine that you've seen, for the valsartan</p> <p>24 manufacture with the zinc chloride process at any</p>	<p style="text-align: right;">Page 333</p> <p>1 to sent out another file which I don't see?</p> <p>2 Q. I don't know. I haven't decided</p> <p>3 yet.</p> <p>4 A. Oh, okay.</p> <p>5 Q. Not sure.</p> <p>6 Did you read Min Li's testimony</p> <p>7 where he testified to what the e-mail said?</p> <p>8 MR. BERNARDO: Object to the</p> <p>9 form of the question. Asked and</p> <p>10 answered.</p> <p>11 THE WITNESS: As I said, if</p> <p>12 you, you know, if you have a document,</p> <p>13 I'd like to see it because then we both</p> <p>14 are clear what we talk about here.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. I'm talking about the deposition of</p> <p>17 Min Li.</p> <p>18 A. Right.</p> <p>19 Q. Did you read the part where he told</p> <p>20 us under oath, speaking for ZHP as a corporate</p> <p>21 representative, what the e-mail said?</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. If there's a</p> <p>24 portion of the testimony you're asking if</p>

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1 he's read, it would be helpful to show
2 him.

3 THE WITNESS: I -- I read
4 from Min Li's testimony, but I really
5 don't know what line or what section you
6 refer to. It's hard for me to -- to
7 actually speculate.

8 BY MR. SLATER:

9 Q. I'm looking at your report. Why
10 don't we look at your report. You have your hard
11 copy of your report right there. Let's go to page
12 54.

13 You see your report page 54? You
14 have that in front of you?

15 A. Yes.

16 Q. Okay. And right in the middle of
17 the page Section VII, you say in the first
18 sentence that:

19 "Plaintiffs' experts assert that, in
20 an e-mail dated July 27, 2017, ZHP employee
21 Jinsheng Lin 'acknowledged the impurity he was
22 investigating [in crude irbesartan] was very
23 likely an 'N-NO compound' which 'is similar to the
24 N-nitrosodimethylamine that occurs in valsartan

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1 when quenched with sodium nitrite."
2 Do you see that?

3 A. I saw that quote.

4 Q. And did you read the actual e-mail?

5 A. I -- I -- I read the e-mail. I
6 would -- I think the e-mail if you -- the e-mail
7 was in both Chinese and then English like a
8 version.

9 Yeah, I remember reading the e-mail.

10 Q. Okay. And you say in your report on
11 page 55:

12 "Mr. Lin's e-mail is written in
13 Chinese, my native language."

14 So then you say:

15 "Based on my understanding of
16 Chinese and my expertise as a chemist" and then
17 you go on.

18 So the question I want to ask you
19 is: In terms of your interpretation of the
20 e-mail, you're relying on your reading of the
21 document in Chinese and your expertise as a
22 chemist in order to interpret it, correct?

23 A. Well, not just that. I also
24 considered the translate -- translates I got from

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1 the counsel.

2 Q. Did you also consider Min Li's
3 testimony as to what the e-mail actually said when
4 he was deposed under oath as a corporate
5 representative speaking for ZHP?

6 MR. BERNARDO: Object to the
7 form of the question. Vague.

8 THE WITNESS: So, yeah. So
9 it's better that you highlight what he
10 said. I remember reading his
11 testimonies, but I don't know what
12 section you refer to.

13 BY MR. SLATER:

14 Q. Well, you didn't actually --
15 rephrase. Hang on.

16 You actually didn't talk in your --
17 rephrase.

18 You didn't actually quote what
19 Dr. Li said in his testimony, right? That's not
20 quoted in your report, right?

21 A. I didn't.

22 Q. When you interpreted what the e-mail
23 said, did you rely on your own reading of the
24 e-mail, or did you rely on Dr. Li's reading of the

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1 e-mail which he testified to under oath on behalf
2 of ZHP?

3 MR. BERNARDO: Object to the
4 form of the question. Vague.

5 THE WITNESS: I mean, for
6 this e-mail, I read in different format,
7 right? They all be kind of different.
8 And then I -- what I read, truthfully,
9 what I did is, I went in to see what the
10 whole article -- what the whole document
11 was really talk about in science.

12 Because I, you know, I'm an
13 organic chemist. I want to learn because
14 there are confusions. I have to admit
15 there are confusions for me. I don't
16 really understand some part of this in
17 detail.

18 So I just went in as a
19 scientist to see what the science told
20 me. And then I also, you know, I
21 remember that e-mail also had -- had a --
22 had an attachment in there.

23 I -- I specifically asked the
24 counsel to provide that attachment to me.

<p style="text-align: right;">Page 338</p> <p>1 I also read that attachment. I</p> <p>2 believe -- I might be wrong in this. But</p> <p>3 I believe the attachment only -- I don't</p> <p>4 remember reading in Chinese. Probably I</p> <p>5 only read English. I might be wrong on</p> <p>6 that.</p> <p>7 But, anyway, so my -- my -- my</p> <p>8 -- my opinion was formed solely just</p> <p>9 based on my understanding of the</p> <p>10 chemistry of the two full document</p> <p>11 together to reach to the conclusion.</p> <p>12 I don't remember quoting</p> <p>13 anybody because I, you know, I don't want</p> <p>14 to kind on anybody side. I just want to</p> <p>15 see what the science taught me about.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Were you aware when you formed your</p> <p>18 opinion about what the e-mail said and meant that</p> <p>19 Dr. Li's testimony as a corporate representative</p> <p>20 of ZHP was binding on ZHP?</p> <p>21 MR. BERNARDO: Object to form.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. Were you aware of that?</p> <p>24 MR. BERNARDO: Object to the</p>	<p style="text-align: right;">Page 340</p> <p>1 that it is binding, which is legal.</p> <p>2 MR. SLATER: Do you want to</p> <p>3 take the position that your corporate</p> <p>4 representative's testimony is not binding</p> <p>5 on your client? I guess you can kind of</p> <p>6 float that one when we get to court.</p> <p>7 MR. BERNARDO: I want to take</p> <p>8 the position that it's inappropriate to</p> <p>9 ask a legal conclusion about binding form</p> <p>10 of testimony.</p> <p>11 MR. SLATER: Okay. You made</p> <p>12 your objection. You got your objection.</p> <p>13 BY MR. SLATER:</p> <p>14 Q. Doctor, were you aware -- rephrase.</p> <p>15 Did anybody ever inform you that Min</p> <p>16 Li testified for ZHP as a representative and his</p> <p>17 testimony was binding on ZHP when you were making</p> <p>18 choices as to which version of what the e-mail</p> <p>19 said you should rely on?</p> <p>20 I just want to know if you knew</p> <p>21 that.</p> <p>22 MR. BERNARDO: Object to the</p> <p>23 form of the question. Vague. Calls for</p> <p>24 legal conclusion.</p>
<p style="text-align: right;">Page 339</p> <p>1 form of the question. Legal conclusion.</p> <p>2 And still vague as to the reference to</p> <p>3 the testimony.</p> <p>4 THE WITNESS: Well, I can only</p> <p>5 say when I -- when I --</p> <p>6 BY MR. SLATER:</p> <p>7 Q. I just want to know if you knew that</p> <p>8 Dr. Li's testimony was binding on ZHP. All of his</p> <p>9 testimony -- because he testified as a corporate</p> <p>10 representative -- that it was binding, and he was</p> <p>11 speaking for the company.</p> <p>12 Did you know that?</p> <p>13 MR. BERNARDO: Object to the</p> <p>14 form of the question. It's a legal</p> <p>15 conclusion. Dr. Xue is, as we know, not</p> <p>16 a lawyer and --</p> <p>17 MR. SLATER: I'm asking if</p> <p>18 anyone told him that. I didn't ask if he</p> <p>19 agrees. So I'm not sure what the</p> <p>20 objection is.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Can you answer, Doctor? Did anyone</p> <p>23 ever tell you that?</p> <p>24 MR. BERNARDO: You concluded</p>	<p style="text-align: right;">Page 341</p> <p>1 BY MR. SLATER:</p> <p>2 Q. It's a yes or no. Did anyone tell</p> <p>3 you that?</p> <p>4 A. I -- I don't remember anybody told</p> <p>5 me that.</p> <p>6 Q. Okay.</p> <p>7 A. But I...</p> <p>8 Q. Did anybody ever give you the typed</p> <p>9 transcription in English that ZHP presented to the</p> <p>10 court as their official transcription of the</p> <p>11 e-mail?</p> <p>12 MR. BERNARDO: Object to the</p> <p>13 form.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. Translation I should say.</p> <p>16 MR. BERNARDO: Object.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. Let me ask it again.</p> <p>19 Did anybody ever give you the</p> <p>20 translation that ZHP produced to the court as a</p> <p>21 true and accurate copy of an English language</p> <p>22 translation of the July 27, 2017 e-mail, which ZHP</p> <p>23 presented to the court? Did you ever get that</p> <p>24 translation?</p>

<p style="text-align: right;">Page 342</p> <p>1 MR. BERNARDO: Object to the 2 form of the question and the 3 characterization of it. Document. 4 Assumes facts. 5 THE WITNESS: Well, as I said 6 just now, right? This I -- I read. 7 Honestly, I never ask what translate 8 those are, but I was -- I read two 9 translate along with original Chinese. 10 I told you just now. I was 11 confused for many points. The translate 12 help a little bit but not really much. 13 So I solely -- as I said, I 14 solely just rely on my expertise of the 15 organic chemistry, which I'm here for, 16 right? 17 So I understand what the 18 author of the e-mail was trying to do 19 through -- throughout his own, the full 20 -- the full document and along with the 21 attachment was what was put in there. 22 So to answer your question, I 23 don't know exactly which one you talk 24 about. Which one. Trying to say what, I</p>	<p style="text-align: right;">Page 344</p> <p>1 Lin" then there's a Bates number "is attached to 2 this Declaration as Exhibit K." 3 MR. BERNARDO: Object to the 4 form of the question. Object to asking 5 this witness about a legal document. 6 MR. SLATER: I'm literally 7 just showing him where it came from, 8 Rich. 9 MR. BERNARDO: May I finish my 10 objection and you can ask whatever you 11 want. 12 Object on the grounds of 13 foundation. 14 Go ahead, Doctor. 15 MR. SLATER: You're objecting 16 on the grounds of foundation? What's 17 that? Tell me that one so I understand 18 how to ask a better foundation question 19 when I literally just showed him the 20 declaration and the paragraph identifying 21 the exhibit. Tell me what the issue with 22 foundation is so I can fix my question. 23 MR. BERNARDO: Whether this 24 witness has even seen this document.</p>
<p style="text-align: right;">Page 343</p> <p>1 don't know that. 2 Are you -- are you adding a 3 new file to my folder? 4 (Audio malfunction). 5 (Document marked for 6 identification as Xue Exhibit 15.) 7 MR. SLATER: All right. I 8 think I just said a whole bunch of stuff 9 and no one heard it. 10 MR. BERNARDO: That is 11 correct. If you said anything, nobody 12 heard it. 13 MR. SLATER: Which is probably 14 ideal. 15 Chris, can you go back to the 16 certification? To the paragraph K, or 17 paragraph whatever that was, 13. 18 BY MR. SLATER: 19 Q. All right. Looking at paragraph 13 20 of Seth Goldberg's declaration, which is dated 21 May 14, 2021, you see paragraph 13 which says: 22 "A true and correct copy of an 23 English language translation of an e-mail dated 24 July 27, 2017, authored by ZHP employee Jinsheng</p>	<p style="text-align: right;">Page 345</p> <p>1 MR. SLATER: That's not a 2 legitimate -- 3 MR. BERNARDO: Or whether he 4 knows what it is. 5 MR. SLATER: That's not a 6 legitimate objection. 7 MR. BERNARDO: I disagree. 8 Go ahead. 9 MR. SLATER: Okay. Whether 10 he's seen it is a foundation objection? 11 Haven't even asked him that. 12 All right. I'm going to move 13 along. I'm confident in this question. 14 BY MR. SLATER: 15 Q. So now I'm going to show you Exhibit 16 K, okay, Dr. Xue? Exhibit K -- let's go to the 17 document -- is right there on the screen. And at 18 the top it says: 19 "Bulletin on the preliminary 20 findings about produced unknown impurities in 21 quenching sodium azide for the crude irbesartan." 22 Do you see that? 23 A. Can you make this -- make this 24 bigger?</p>

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1 Yeah, I -- as I said, I read.
 2 Q. It's right there on the screen.
 3 A. Yeah.
 4 Q. Do you see? Do you see the e-mail?
 5 A. I read -- this is translate, not
 6 original e-mail, right? So I saw --
 7 Q. Have you seen this translation?
 8 That's -- let me start with a new
 9 question.
 10 Have you seen this translation?
 11 A. It's really hard for me to answer
 12 this question because I, you know, I read so many
 13 things, and this for this particular document, I
 14 know for sure I read more than one English
 15 translate. I have to kind of read through to see
 16 whether I saw this.
 17 Q. Doctor, fine. You're not sure if
 18 this is the translation you saw.
 19 Let's go to page 2, and at the top
 20 of page 2, it says:
 21 "Through the secondary mass
 22 spectrometry analysis, it can be inferred that the
 23 additional NO substituent is in the cyclic
 24 compound fragment part, and it is probably that it

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1 is the N-NO compound."
 2 I want to stop there.
 3 You see what I just read, that first
 4 part of the sentence at the top of the page?
 5 A. I -- I saw what you read.
 6 Q. Okay. So you can see they refer to
 7 the fact that they used mass spectrometry, right?
 8 MR. BERNARDO: Object to the
 9 form of the question. Vague.
 10 BY MR. SLATER:
 11 Q. I'll ask the question again.
 12 You see that Dr. Lin who wrote the
 13 e-mail refers to a mass spectrometry analysis?
 14 You see that, right?
 15 A. I saw, yes.
 16 Q. Now, going back to where I left off.
 17 After it talks about what they were seeing in the
 18 irbesartan that they were working on, it says:
 19 "Similar to the
 20 N-nitrosodimethylamine group produced by the
 21 quenching of valsartan with sodium nitrite, its
 22 structure is very toxic, and its possible
 23 production pathways are as follows."
 24 Okay. I want to stop there.

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1 Do you see what I just read?
 2 Do you see what I just read?
 3 A. (Reviews document.)
 4 Q. Doctor, are you there?
 5 A. That's the first paragraph still,
 6 right?
 7 Q. Yeah, it's the first paragraph.
 8 A. Yes, it is what you just read, but
 9 this is one --
 10 Q. Doctor, that's what I asked you.
 11 Do you see what I just read?
 12 A. Yes.
 13 Q. So in this translation provided by
 14 ZHP, in part Dr. Lin pointed out that there is an
 15 N-nitrosodimethylamine group produced by the
 16 quenching of valsartan with sodium nitrite.
 17 That's what it says on the paper,
 18 correct?
 19 MR. BERNARDO: Object to the
 20 form of the question.
 21 BY MR. SLATER:
 22 Q. That's what the words on the page
 23 say, correct?
 24 A. I -- I --

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1 Q. Is that what the words on the page
 2 say?
 3 A. Honestly, I don't think.
 4 Q. You don't think.
 5 Is that what words on the page say,
 6 Doctor?
 7 A. But this is not my approach. I'm
 8 here to offer --
 9 Q. Doctor, I'm not asking your
 10 approach. I'm taking -- I'm taking this
 11 deposition. You filibustered me for like half the
 12 deposition.
 13 MR. BERNARDO: Okay. Let's --
 14 BY MR. SLATER:
 15 Q. I'm not really that bitter about it
 16 because it's Friday so we're all happy people, but
 17 I asked you a very simple question.
 18 Do you see the words on the page
 19 showed what I just showed you?
 20 MR. BERNARDO: Object to the
 21 form of the question. Object to the
 22 argumentative nature of the question.
 23 Dr. Xue, he's just asking you
 24 to agree or disagree that he read that

<p style="text-align: right;">Page 350</p> <p>1 properly from what's on the page.</p> <p>2 THE WITNESS: Sorry, Rich.</p> <p>3 Can you repeat what you said? Because</p> <p>4 you were just -- I didn't hear any</p> <p>5 basically.</p> <p>6 MR. BERNARDO: Dr. Xue, he's</p> <p>7 just asking you if you agree that he read</p> <p>8 what's on the page correctly.</p> <p>9 THE WITNESS: Oh, by reading,</p> <p>10 yes, I don't have any problem with the</p> <p>11 reading part.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. So in this e-mail, according to the</p> <p>14 translation from ZHP, Dr. Lin pointed out that</p> <p>15 there's NDMA in valsartan and it's produced by the</p> <p>16 quenching of valsartan with sodium nitrite.</p> <p>17 That's what that phrase says,</p> <p>18 correct?</p> <p>19 MR. BERNARDO: Object to the</p> <p>20 form of the question. Assumes facts.</p> <p>21 Go ahead, Dr. Xue.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. That's what it says, right?</p> <p>24 A. That's -- that's one form of the</p>	<p style="text-align: right;">Page 352</p> <p>1 I mean, I -- I speak Chinese, right?</p> <p>2 So it's Chinese sometimes -- how to say this?</p> <p>3 It's not -- it's not like you can word to word</p> <p>4 translate things and say, oh, this must be</p> <p>5 accurate, right?</p> <p>6 I didn't ask, but I assume</p> <p>7 everything provided to me, they are not just</p> <p>8 random translate. They are -- they are -- they</p> <p>9 must be some, you know, certified translate and</p> <p>10 then provide that to me, right?</p> <p>11 So everybody's translate has some</p> <p>12 value there. I can't answer this particular one</p> <p>13 at all. I'm not saying that or any other ones I</p> <p>14 saw.</p> <p>15 So what I really, my portion, I</p> <p>16 mention that, right? I went to the science. They</p> <p>17 talk about irbesartan, right? That clearly show</p> <p>18 in their theme, they talk about reaction happened</p> <p>19 on irbesartan. And then, too, as example to show</p> <p>20 this might be a common, common, possible common</p> <p>21 reaction.</p> <p>22 He also in his attachment showed</p> <p>23 this particular reaction also happen on the drug</p> <p>24 molecule. In this case, it's a deoscillated</p>
<p style="text-align: right;">Page 351</p> <p>1 translation, right? So if you look at other</p> <p>2 translation, they are different forms. And plus,</p> <p>3 even if just this -- this form of translation,</p> <p>4 right, that -- that N-nitrosodimethylamine group</p> <p>5 is not talk about NDMA. It talk about a group</p> <p>6 that is similar to NDMA.</p> <p>7 So what I really trying to say is,</p> <p>8 you know, if you put up one thing and to say</p> <p>9 whether this is read correct or this or that, I</p> <p>10 don't think that's a complete understanding of</p> <p>11 what the e-mail is.</p> <p>12 And point out. When I read this, I</p> <p>13 first read in Chinese. I found there are puzzles</p> <p>14 I cannot read and understand, and then I went</p> <p>15 through the science.</p> <p>16 I went through all the translate</p> <p>17 that provide to me, too. That explains some, but</p> <p>18 really not help me to -- to grab the whole</p> <p>19 information.</p> <p>20 I mean, I'm here as an organic</p> <p>21 chemist, right, trying to offer my opinion with a</p> <p>22 neutral way, but I don't think it's right that</p> <p>23 when you have multiple of these translate, you</p> <p>24 point one to say, is this word correct or not?</p>	<p style="text-align: right;">Page 353</p> <p>1 irbesartan -- sorry -- valsartan.</p> <p>2 The common theme as I show in -- see</p> <p>3 there in my report carefully I say, okay, so this</p> <p>4 is what he actually really mean to show. There's</p> <p>5 a reaction definite on this reactive nitrogen on</p> <p>6 this particular drug, irbesartan, and also this</p> <p>7 can be a general or a common theme when you have a</p> <p>8 similar reactive, a group of nitrogen atom on</p> <p>9 deoscillated valsartan and that can be actually</p> <p>10 parallel.</p> <p>11 He -- I honestly I have no clue how</p> <p>12 he actually hypothesized these things are highly</p> <p>13 toxic. That's where -- where my puzzle come from.</p> <p>14 I don't know. I mean, I respect everybody, but</p> <p>15 this person, this Dr. Jinsheng Li, I don't see he</p> <p>16 show any evidence to me showing either one of</p> <p>17 these compound are highly toxic.</p> <p>18 Because, you know, you cannot assume</p> <p>19 nitroso-compound are highly toxic. He put in</p> <p>20 there. That confuse me a lot.</p> <p>21 But I can only say my point or my</p> <p>22 conclusion or my opinion is, he's talked about</p> <p>23 irrelevant reaction, and that reaction can be a</p> <p>24 common theme as he warn his boss or, you know.</p>

<p style="text-align: right;">Page 354</p> <p>1 Yeah. So in the e-mail say, okay, 2 look, there might be something we pay attention. 3 That's all I learn from -- from -- from the whole 4 thing. 5 I really don't want to get involved 6 in this, like, look at this particular one 7 translate, tell me if this is correct. 8 Yes, I'm Chinese. 9 Q. Doctor, are you just going to talk 10 until my time is up? I mean, is that what you're 11 trying to do? 12 A. I'm trying to help. I really 13 offered -- 14 Q. You're not helping. You're not 15 helping. You're not -- you're not anywhere close 16 to helping. With all due respect, I don't know 17 what you're doing. 18 You're talking about -- you're like 19 off in all different places. I don't even know 20 what you're talking about. I'm just being really 21 honest. I don't know what you're doing. 22 A. Well, I -- 23 MR. BERNARDO: Dr. Xue. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 356</p> <p>1 That's a true statement with regard 2 to the zinc chloride process, right? 3 MR. BERNARDO: Object to the 4 form of the question. Assumes facts. 5 BY MR. SLATER: 6 Q. It's a true statement, right? 7 You already told me that's -- 8 that's -- that's how it was caused. That's the 9 point when the NDMA was created during the 10 quenching, right? 11 A. No, I didn't. 12 Q. Yes or no. 13 A. I didn't. 14 Q. Hold on. Stop. Stop. You 15 disagree. 16 So now your opinion is that the NDMA 17 in the zinc chloride process didn't form during 18 the quenching process. 19 Is that now -- you're now -- you 20 don't agree with that? Yes or no. 21 A. Sorry. I'm laughing. 22 Q. There's no more speeches, Doctor. 23 The speech part of the day is over. So you're 24 going to give direct answers, please.</p>
<p style="text-align: right;">Page 355</p> <p>1 Q. I don't even know what you're 2 talking about anymore, Doctor. I'm totally 3 baffled. You've baffled me. 4 MR. BERNARDO: It's late on a 5 Friday afternoon. Let's just, Dr. Xue -- 6 MR. SLATER: I'm laughing. I 7 mean, I'm actually smiling. I'm not 8 yelling at him. 9 MR. BERNARDO: I know. Adam, 10 I'm not accusing you of yelling. 11 MR. SLATER: I think I'm being 12 a pretty good sport under the 13 circumstances. 14 MR. BERNARDO: Dr. Xue, just 15 please listen to Mr. Slater's questions 16 and try and answer them as best you can. 17 I know it's late. I know you're not 18 feeling well. 19 Adam. 20 BY MR. SLATER: 21 Q. Okay. Dr. Xue, it was a true 22 statement when Dr. Lin said it that 23 N-nitrosodimethylamine was produced by the 24 quenching of valsartan with sodium nitrite.</p>	<p style="text-align: right;">Page 357</p> <p>1 A. All right. 2 Q. It's a very simple question. 3 Do you agree or disagree that the 4 NDMA formed in the zinc chloride process during 5 the sodium nitrite quenching step? 6 A. After 2018 when the whole thing 7 start to show, everybody including myself learned 8 NDMA can form during this process. 9 Q. Thank you. 10 A. I never talk about this. 11 Q. So -- 12 A. But now we look at the e-mail was 13 prior to that. 14 Q. Doctor, you got to -- 15 MR. SLATER: Rich, I'm not 16 going to let him do this. 17 MR. BERNARDO: Dr. Xue. 18 Dr. Xue. 19 MR. SLATER: I'm not going to 20 let him do this anymore. 21 MR. BERNARDO: Okay. Adam, 22 can we just take a brief break and I'll 23 see if I can -- 24 MR. SLATER: I mean, I'd</p>

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1 rather not do it in the middle of going
2 through this e-mail segment.
3 MR. BERNARDO: Yeah, I know.
4 Further --
5 MR. SLATER: I really wanted
6 to. You could tell him on the record to
7 stop giving speeches and just answer my
8 questions.
9 MR. BERNARDO: I'm not going
10 to say.
11 Dr. Xue, I know it's late.
12 Just please listen to Mr. Slater's
13 questions. If there's more to add, I'm
14 permitted to ask you after Mr. Slater is
15 done and you can add it then.
16 So, please, just answer
17 Mr. Slater's questions. I know this is
18 confusing with the translations and it's
19 late.
20 BY MR. SLATER:
21 Q. All right. Let's be very clear.
22 In the zinc chloride process --
23 A. Right.
24 Q. -- do you agree that the NDMA formed

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1 when the quenching occurred with the sodium
2 nitrite? Is that when the NDMA formed?
3 A. Now, yes, everybody learn.
4 Q. Okay. In July of 2017, that's what
5 Dr. Lin said in this e-mail -- it's right there in
6 front of you -- that the NDMA produced by the
7 quenching of valsartan with sodium nitrite. He
8 said that in 2017.
9 You see that right in front of you,
10 correct?
11 MR. BERNARDO: Object to the
12 form of the question. Assumes facts.
13 Asked and answered. Mischaracterizes his
14 prior testimony about that sentence.
15 THE WITNESS: I disagree.
16 Because as I said, you know, this is one
17 form of the translate. And even the
18 original Chinese when I read, I was
19 confused.
20 I -- I read more than this. I
21 don't know. This might be one of the two
22 that I read. This might be the third one
23 that I read. I -- I cannot remember
24 exactly, but I cannot just look at one

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1 translate, word by word translate to say
2 this is about NDMA, right?
3 So I remember clearly there's
4 one translate. They have a different
5 translate there as well.
6 BY MR. SLATER:
7 Q. How many translations did you see?
8 A. Well, I honestly don't remember. I
9 think two.
10 Q. Was this one?
11 A. I don't know it's one of the two. I
12 -- I don't remember.
13 Q. Okay. Now, let's scroll down to the
14 bottom half. Underneath the little diagrams, the
15 second paragraph. It says in the second sentence
16 of the second paragraph down there:
17 "This is a common problem in the
18 production and synthesis of sartan API."
19 Do you see that?
20 MR. BERNARDO: Object to the
21 form of the question. Same objection
22 with respect to the use of this document.
23 BY MR. SLATER:
24 Q. Do you see the sentence I just read?

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1 A. By reading, yes.
2 Q. So according to this e-mail as
3 translated by ZHP, Dr. Lin advised in the e-mail
4 that this problem with the creation of
5 N-nitrosodimethylamine group due to quenching of
6 Valsartan with sodium nitrite is a common problem
7 in the production and synthesis of sartan API,
8 correct?
9 MR. BERNARDO: Object to the
10 form of the question.
11 BY MR. SLATER:
12 Q. That's what the e-mail says, right?
13 MR. BERNARDO: Object to the
14 form of the question. The
15 characterization of the document. It
16 assumes facts.
17 Go ahead, Dr. Xue.
18 THE WITNESS: I disagree as
19 I --
20 BY MR. SLATER:
21 Q. Fine. You disagree.
22 Based on your interpretation, right?
23 A. Based on my understanding of the
24 whole article -- the whole e-mail with the

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1 attachment.

2 Q. Which includes your own

3 interpretation and translation of the e-mail based

4 on your reading of the Chinese language, right?

5 A. Based on my reading of everything,

6 not just the Chinese. Also every translate that

7 provide to me. Also the reference that attached

8 to this e-mail as well. That's -- that's how I

9 define myself.

10 Q. Okay. He then says:

11 "It is recommended to improve to

12 other quenching method, such as NaClO, in addition

13 to optimize the quenching process for sodium azide

14 in valsartan."

15 So he's literally pointing out we

16 need to optimize the quenching because he's

17 pointed out that the quenching of the sartans is

18 causing nitrosamines to form.

19 That was a good suggestion, right?

20 Let's optimize the quenching so we don't create

21 nitrosamines. That was a smart suggestion,

22 correct?

23 MR. BERNARDO: Object to the

24 form of the question, to the use of this

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1 document, to the translation, and to the

2 characterization of his prior testimony.

3 Go on.

4 THE WITNESS: Well, something

5 Dr. Jinsheng Lin is talking here. I

6 never against that. I think that's my

7 understanding as well.

8 However, the reaction he refer

9 to here, also clearly to me after I read

10 the whole thing and I see the whole

11 situation is the reaction to form what he

12 join up there, the nitroso-compound.

13 Also, the deoscillated

14 valsartan in that patent also can form a

15 nitroso-compound. These two compounds he

16 hypothesized can be, and he then offered

17 a potential optimization. Say, hey, if

18 we not using the quenching, using other

19 quenching as people already reported in

20 their patent, we might be able to get

21 around these potential -- potential

22 nitroso-compound that he raised.

23 I think that I agree with you.

24 To look for a different quenching process

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1 is what he offered to do. I think to me

2 it's definitely some option you can

3 actually consider to do that that's --

4 that's one of them.

5 But the two reaction they talk

6 about is actually these two I mention.

7 Sorry I confuse you first place, but

8 it's --

9 BY MR. SLATER:

10 Q. It's not confusing me, Doctor.

11 You're just eating all my time up.

12 A. But these are the two reactions he

13 talk about, and so he -- he suspect these two

14 compound, nitroso-compounds, they can be highly

15 toxic, which I don't agree. I don't know where he

16 gets supported from.

17 But I think as an employee seeing

18 nitroso-compound like these two and warn his boss

19 about this as a potential and then suggest some

20 potential solution for this, I feel this --

21 this -- this is logic.

22 Q. If we go down to the last paragraph,

23 he talks about the patent?

24 A. Right.

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1 Q. He talks about the fact that they

2 proposed that the use of NaNO₂ -- that's sodium

3 nitrite, right?

4 A. Correct.

5 Q. That sodium nitrite quenching will

6 produce N-NO impurities. And then he says:

7 "In the meanwhile, our Huahai crude

8 valsartan was detected by LC-MS."

9 Do you see that?

10 A. Correct.

11 Q. So he's pointing out that the

12 nitroso-compound that they detected in their

13 valsartan, they detected it with LC-MS.

14 That's what he's saying, correct?

15 A. What they were saying is the

16 deoscillated valsartan. As I show you in my

17 report, right? That compound can be nitrosamine.

18 So that's the compound they talk.

19 I just want to make -- make it clear

20 what we talk about here. They not talk about

21 valsartan the drug itself get nitrosylate. To my

22 knowledge today they ask me there still be no

23 chance that you can do nitrosylation on valsartan

24 drug itself. That's my -- my -- my honest

<p style="text-align: right;">Page 366</p> <p>1 feeling.</p> <p>2 What the patent does and what the</p> <p>3 patent show us is this compound deoscillated</p> <p>4 valsartan can actually get nitrosylation reaction</p> <p>5 to give you this. I believe they call it impurity</p> <p>6 K maybe, right? So they -- they talk about that,</p> <p>7 right?</p> <p>8 So it's not talk about valsartan at</p> <p>9 all or anything about even. This -- this whole</p> <p>10 art -- this whole document has nothing to do with</p> <p>11 NDMA or NDEA.</p> <p>12 Q. Well, where he says -- let's go back</p> <p>13 up to the top of the document. Then we'll move to</p> <p>14 something else.</p> <p>15 Where he says that what he was</p> <p>16 seeing in the irbesartan was similar to the NDMA</p> <p>17 produced by the quenching of valsartan with sodium</p> <p>18 nitrite, that's relevant to this case, right?</p> <p>19 MR. BERNARDO: Object to the</p> <p>20 form of the question and the</p> <p>21 characteration -- characterization of the</p> <p>22 documents being used.</p> <p>23 Go on.</p> <p>24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 368</p> <p>1 A. No. No. I have to -- I have to be</p> <p>2 clear.</p> <p>3 Q. No. No, Doctor, we're not. You</p> <p>4 don't get -- you don't get to run the deposition.</p> <p>5 That's what it says. It says quenching of</p> <p>6 valsartan.</p> <p>7 MR. BERNARDO: He's trying to</p> <p>8 explain why he disagrees.</p> <p>9 MR. SLATER: This is -- he</p> <p>10 disagrees that the word says "valsartan"?</p> <p>11 MR. BERNARDO: Let him finish</p> <p>12 his answer and he'll explain what he</p> <p>13 means.</p> <p>14 MR. SLATER: You know what? I</p> <p>15 withdraw the question. So we're not</p> <p>16 going to hear the speech.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. If I'm correct that Jinsheng Lin</p> <p>19 said in this e-mail that there was NDMA in</p> <p>20 valsartan and it was formed by sodium nitrite</p> <p>21 quenching, and that was known in July of 2017,</p> <p>22 does that impact any of your opinions?</p> <p>23 If that's the case, does that impact</p> <p>24 any of your opinions in this case?</p>
<p style="text-align: right;">Page 367</p> <p>1 Q. That's present -- that's relevant to</p> <p>2 the case, right?</p> <p>3 What was happening with valsartan</p> <p>4 and how the NDMA was formed, that's relevant,</p> <p>5 right?</p> <p>6 MR. BERNARDO: Same</p> <p>7 objections.</p> <p>8 THE WITNESS: Even if -- even</p> <p>9 if we only look at this translate, right,</p> <p>10 not consider any other things. First of</p> <p>11 all, I think that's biased already.</p> <p>12 Even if this, they clearly</p> <p>13 talk about the compound happen during the</p> <p>14 valsartan process where the deoscillated</p> <p>15 valsartan can actually react to form a</p> <p>16 nitroso-compound. These are --</p> <p>17 BY MR. SLATER:</p> <p>18 Q. I'm sorry, Doctor.</p> <p>19 Where does he say -- where does he</p> <p>20 say valsartan -- deoscillated valsartan?</p> <p>21 It says "quenching of valsartan with</p> <p>22 sodium nitrite."</p> <p>23 That's what it says in those words,</p> <p>24 right?</p>	<p style="text-align: right;">Page 369</p> <p>1 MR. BERNARDO: Object to form.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. Yes or no. It's a simple yes-or-no</p> <p>4 question.</p> <p>5 MR. BERNARDO: Object to the</p> <p>6 form of the question. It calls for</p> <p>7 speculation. Assumes facts.</p> <p>8 Go on.</p> <p>9 THE WITNESS: Well, you said a</p> <p>10 lot of assumptions, right? Let me -- let</p> <p>11 me walk through this.</p> <p>12 You said if I -- if I -- if I</p> <p>13 just --</p> <p>14 BY MR. SLATER:</p> <p>15 Q. You don't understand the question.</p> <p>16 I'll ask it again. I didn't have a lot of</p> <p>17 assumptions. Let me ask it again.</p> <p>18 Well, let me ask you this.</p> <p>19 In July of 2017, there was NDMA in</p> <p>20 the valsartan manufactured with the zinc chloride</p> <p>21 process, and as we talked about before, the NDMA</p> <p>22 formed during the sodium nitrite quenching, right?</p> <p>23 A. So after all these analysis, yes, we</p> <p>24 now know that at that time or even earlier it was</p>

<p style="text-align: right;">Page 370</p> <p>1 formed. But nobody knows till 2018, right.</p> <p>2 Q. Well, if I'm correct -- well,</p> <p>3 rephrase.</p> <p>4 If Min Li is correct in how he</p> <p>5 translated the document when he read it under oath</p> <p>6 for ZHP that the e-mail said that what they were</p> <p>7 seeing in the irbesartan was similar to the NDMA</p> <p>8 in valsartan which was created by the sodium</p> <p>9 nitrite quenching, if that is what the e-mail</p> <p>10 said, then people within ZHP knew about the issue</p> <p>11 with the NDMA in July of 2017, correct?</p> <p>12 MR. BERNARDO: Object to the</p> <p>13 form of the question. Vague. Object to</p> <p>14 the characterization of Min Li's</p> <p>15 testimony. Assumes facts.</p> <p>16 Go ahead, Dr. Xue.</p> <p>17 THE WITNESS: Well, I think I</p> <p>18 read Min Li's depositions. I read -- I</p> <p>19 don't remember exactly what he said.</p> <p>20 I don't think your</p> <p>21 characterization saying he agreed with</p> <p>22 everything that you just said. I don't</p> <p>23 remember it clearly get that sense. I</p> <p>24 remember he somehow -- I don't know</p>	<p style="text-align: right;">Page 372</p> <p>1 Q. If ZHP knew -- rephrase.</p> <p>2 If Jinsheng Lin -- well, rephrase.</p> <p>3 I'll ask it straight-out.</p> <p>4 If the e-mail says that -- I'll ask</p> <p>5 it even differently.</p> <p>6 If ZHP knew that there was NDMA in</p> <p>7 the valsartan as of July 2017 and never disclosed</p> <p>8 it, that would be inexcusable, right?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question. Argumentative.</p> <p>11 Listen to his question,</p> <p>12 Dr. Xue.</p> <p>13 THE WITNESS: So you're</p> <p>14 asking if -- if -- if ZHP knew NDMA</p> <p>15 present prior to this e-mail? Was that</p> <p>16 your question? Then they will be</p> <p>17 inexcusable? That was -- that was what</p> <p>18 you asking?</p> <p>19 BY MR. SLATER:</p> <p>20 Q. If ZHP knew there was NDMA in the</p> <p>21 valsartan in July of 2017 or earlier and didn't</p> <p>22 tell anybody, that would be inexcusable, right?</p> <p>23 A. If that's the case, yes.</p> <p>24 Q. And you're just trying to come to an</p>
<p style="text-align: right;">Page 371</p> <p>1 what -- what -- what translate or whether</p> <p>2 the -- what you are showing or discuss</p> <p>3 with him about any form.</p> <p>4 I don't remember that, but I</p> <p>5 remember he was pretty like -- I don't</p> <p>6 know -- surprised or something. I don't</p> <p>7 know whether he get a chance to read this</p> <p>8 before.</p> <p>9 I just have many questions.</p> <p>10 Like whether he actually considered. I</p> <p>11 mean, you actually showed him the -- the</p> <p>12 attachment. All these I don't know. I</p> <p>13 don't want to speculate.</p> <p>14 As I said, I'm here. I'm an</p> <p>15 expert.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. All right.</p> <p>18 A. I just want to tell the truth on</p> <p>19 what I actually went in to see all these documents</p> <p>20 provide to me. I honestly judge based on my</p> <p>21 understanding of the science. I try to explain to</p> <p>22 you. Although you say I confuse you, but I really</p> <p>23 try my best, right? I wrote that in my report as</p> <p>24 well. Yeah.</p>	<p style="text-align: right;">Page 373</p> <p>1 understanding of what they knew based on your</p> <p>2 reading of multiple translations and your own</p> <p>3 interpretation of the Chinese version of the</p> <p>4 e-mail and whatever else you saw.</p> <p>5 You don't actually have an opinion</p> <p>6 as to what the e-mail really said because you're</p> <p>7 looking at so many different sources of</p> <p>8 translation, right?</p> <p>9 MR. BERNARDO: Object to the</p> <p>10 form of the question. Object to the</p> <p>11 characterization of his prior testimony.</p> <p>12 THE WITNESS: I disagree. I</p> <p>13 think I clearly offered my opinion on</p> <p>14 this one.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. And part of that opinion is based on</p> <p>17 your own reading of the document in Chinese,</p> <p>18 right?</p> <p>19 A. That's definitely part of it.</p> <p>20 There's other parts. All the information. I</p> <p>21 definitely consider everything that -- that came</p> <p>22 to me I asked for together to form my opinion.</p> <p>23 MR. SLATER: Let's take a</p> <p>24 break.</p>

<p style="text-align: right;">Page 374</p> <p>1 THE VIDEOGRAPHER: Time right 2 now is 5:50 p.m. We're off the record. 3 (Recess.) 4 THE VIDEOGRAPHER: Time right 5 now is 5:38 p.m. We're back on the 6 record. 7 BY MR. SLATER: 8 Q. On page 55 of your report at the 9 bottom, in talking about that July 2017 e-mail you 10 say: 11 "In addition, ZHP employees who have 12 testified about the e-mail have made clear that 13 'due to insufficient extent and depth of process 14 research at the early stage, as well as 15 insufficient study and understanding of potential 16 genotoxic impurities, only side reaction product 17 and degradation products were studied' with 18 respect to Irbesartan, and therefore ZHP 'was 19 unaware of the further reaction between 20 degradation products and raw material' related to 21 Irbesartan." 22 Do you see that? 23 A. I do. 24 Q. And you cite in note 122 to Min Li's</p>	<p style="text-align: right;">Page 376</p> <p>1 A. About why they -- they didn't pursue 2 anything on this irbesartan because it's not 3 relevant. 4 Q. Now what we're going to do is, I'm 5 going to go to the testimony you cited, which is 6 Min Li, April 22, 2021, page 528 line 14. 7 And you can see at line 14 it says: 8 "We have on the screen Exhibit 212, 9 which is a report, and the topic title is 10 'Investigation regarding an unknown impurity,' and 11 then in parentheses 'Genotoxic impurity' with 12 regard to valsartan. 13 "Do you see that?" 14 A. Do I have that document also in my 15 folder? 16 Q. I don't know what you're asking me, 17 Doctor, but I'm showing you the transcript right 18 on the screen, please. 19 A. Well, yeah, but can I see the -- the 20 -- you put everything in my -- 21 MR. SLATER: It's there. 22 What exhibit is it? 23 Exhibit 16 is the transcript. 24 (Document marked for</p>
<p style="text-align: right;">Page 375</p> <p>1 deposition transcript. 2 You see that? 3 A. (Reviews document). 4 Q. Doctor, this is your report. It 5 says 122 at the end of the sentence I read at the 6 bottom of the page? 7 A. Yeah. Sorry. Sorry. I was -- 8 Q. That's Min Li's deposition, right? 9 A. Yes. 10 Q. And after you say that in your 11 report, you say: 12 "As a result, Mr. Lin's e-mail 13 discussing Irbesartan could not have been 14 addressing the formation of nitrosamines as a 15 result of the potential degradation of DMF, which 16 is what plaintiffs' experts assert resulted in the 17 formation of nitrosamines during the zinc chloride 18 process for Valsartan API." 19 You see that? 20 A. I saw that. 21 Q. So you're relying in part on that 22 testimony from Min Li for your understanding and 23 interpretation of the e-mail, correct? That's 24 what you're saying in the report?</p>	<p style="text-align: right;">Page 377</p> <p>1 identification as Xue Exhibit 16.) 2 THE WITNESS: Can you please 3 let me know the page number as well? 4 BY MR. SLATER: 5 Q. It's page 528 line 14. 6 A. Well, it is loading on my computer. 7 So give me a second. 8 Still loading, though. 9 Q. That's all right. Take all the time 10 you want. At some point, I'm going to run out. 11 It's okay. 12 A. For some reason, this way it's just 13 loading. The circle is just going. 14 Q. Do whatever you want. Take as long 15 as you want. I mean, it's only -- I've only lost 16 hours in this -- in this deposition already. It's 17 okay. 18 A. Well, this is not me, right? So. 19 Q. I don't really understand why you 20 need to do that. I literally just showed you what 21 you cited in your report, but okay. 22 MR. BERNARDO: Object to the 23 form of the question. I don't think it's 24 inappropriate for witness to actually ask</p>

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1 to see a transcript of what you're
2 showing one page. That's the way it
3 would ordinarily be done if we were in
4 person.
5 MR. SLATER: That's okay. I
6 think I've been extraordinarily easygoing
7 under the circumstances here. I've got a
8 smile on my face. So it's okay.
9 I assume you're going to be
10 reasonable if all of a sudden we get down
11 to my seven hours so we don't have any
12 issues. But, you know, you can do
13 whatever you want.
14 THE WITNESS: For some
15 reason, this -- this document is really
16 loading like right now.
17 MR. SLATER: Shall we keep the
18 clock going while his document is
19 loading? What do you want to do, Rich,
20 just wait until the clock is out?
21 Why don't you let it spin for
22 30 more minutes. Take whatever time you
23 want.
24 MR. BERNARDO: All right.

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1 Adam, come on. Let's just chill here.
2 If you want to go off the clock, go off
3 the clock. It's your deposition. He's
4 entitled to read the document.
5 MR. SLATER: All right. So
6 let's go off the clock and he can read
7 the deposition.
8 Yeah. Let's go off the -- off
9 the clock and you probably should
10 download the transcript I'm told.
11 THE WITNESS: How can I?
12 Because I was -- I was doing everything
13 else today was -- was fine. So only this
14 one 16 when I click it, it just didn't.
15 BY MR. SLATER:
16 Q. If you go to the folder, the
17 document is there and you can download it.
18 MR. HENRY: There's -- there's
19 a G with three periods next to G. Click
20 that and go to options to download it.
21 THE WITNESS: When I click
22 the three dots, it only says the direct
23 link of this. Or I can download all
24 files it says.

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1 Oh, this one. Okay. Let me
2 try this. Okay. I'm downloading now.
3 Okay. Great. It looks like
4 it's downloading. We can go back to
5 talk.
6 MR. BERNARDO: Well, let's
7 wait until you have it, Dr. Xue.
8 THE WITNESS: Oh, okay.
9 I'm opening it.
10 BY MR. SLATER:
11 Q. It's okay.
12 A. Okay. It's up here.
13 MR. BERNARDO: Why don't you
14 get to the page that he's referring to,
15 Dr. Xue.
16 BY MR. SLATER:
17 Q. Yeah, read it. You said you want to
18 read it. It's okay.
19 I'm not on the clock, Doc. You can
20 read the whole deposition if you want. I don't
21 mind.
22 A. (Reviews document.)
23 Yeah, I think I read this page and
24 we can go back to talk because I really want to go

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1 home tonight.
2 Q. I don't care when I go home. I'll
3 work as late as we need to. I honestly don't
4 care. If I get done with you, I'm going to work
5 on other stuff all night. It doesn't matter.
6 A. Please consider I'm still
7 COVID-positive.
8 Q. So are you ready to answer questions
9 about this?
10 A. Yes. Are we back on the clock?
11 Q. Can we go back on?
12 All right. We're going.
13 Looking at the testimony you cited
14 in your report, it refers to the fact that this
15 report that you cited is the "Investigation
16 regarding an unknown impurity" and then
17 parentheses "Genotoxic impurity" with regard to
18 valsartan.
19 You see the testimony says it's a
20 report regarding valsartan, right?
21 A. Right.
22 MR. BERNARDO: Object to the
23 form of the question and the
24 characterization of his testimony.

<p style="text-align: right;">Page 382</p> <p>1 THE WITNESS: Yeah. By</p> <p>2 reading that section on line 14 to 18,</p> <p>3 that was question asked about.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. You said in your report that that</p> <p>6 report that I was asking Dr. Li about had to do</p> <p>7 with irbesartan.</p> <p>8 So when you said that in your</p> <p>9 report, you were incorrect, right?</p> <p>10 MR. BERNARDO: Object to the</p> <p>11 form of the question.</p> <p>12 THE WITNESS: Well, with this</p> <p>13 short time, I really don't recall what I</p> <p>14 was reading when I write that part. I</p> <p>15 cannot say yes or no this easy. Because</p> <p>16 I think my point there was -- was fairly</p> <p>17 clear.</p> <p>18 That whole e-mail case was</p> <p>19 about irbesartan, and then they talk</p> <p>20 about why they didn't do further study</p> <p>21 because it was just a lab scale discovery</p> <p>22 or development, not even in the real</p> <p>23 factory yet. So they decide not pursue</p> <p>24 any further of that.</p>	<p style="text-align: right;">Page 384</p> <p>1 insufficient study and understanding of potential</p> <p>2 genotoxic impurities, only side reaction product</p> <p>3 and degradation products were studied' with</p> <p>4 respect to Irbesartan, and therefore ZHP 'was</p> <p>5 unaware of the further reaction between</p> <p>6 degradation products and raw material' related to</p> <p>7 Irbesartan."</p> <p>8 Then you say:</p> <p>9 "As a result, Mr. Lin's e-mail</p> <p>10 discussing Irbesartan could not have been</p> <p>11 addressing the formation of nitrosamines," etc.</p> <p>12 Okay. So you were -- you were</p> <p>13 basing your opinion in part on that testimony</p> <p>14 relating to irbesartan.</p> <p>15 That's what your report says, right?</p> <p>16 That's what the report says, Doctor,</p> <p>17 right? It says "irbesartan," correct?</p> <p>18 A. Yes, I wrote that.</p> <p>19 Q. Okay. And now let's go to the</p> <p>20 bottom of page 529 line 17, which is part of the</p> <p>21 testimony you cited for this proposition.</p> <p>22 If we look at page 529 line 17, it</p> <p>23 says -- looking at this report about valsartan</p> <p>24 under the heading of 5.2 "Control strategy," it</p>
<p style="text-align: right;">Page 383</p> <p>1 That's what I meant to -- to</p> <p>2 show there.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. You said in your report when you</p> <p>5 were talking about why the e-mail means what you</p> <p>6 think it means and what you told us you think it</p> <p>7 means, that one of the reasons for that was</p> <p>8 because of that testimony from Dr. Li with regard</p> <p>9 to what you thought was a report about irbesartan.</p> <p>10 That's what you said on page 55 and</p> <p>11 56 of your report, correct?</p> <p>12 It's a yes-or-no question. That's</p> <p>13 what you said, right?</p> <p>14 A. I hope it can be a yes-or-no</p> <p>15 question but really is not.</p> <p>16 Q. Is that what you said in your</p> <p>17 report? Did you refer to this as being -- that</p> <p>18 you said witnesses test -- rephrase.</p> <p>19 You said in your report on bottom of</p> <p>20 55:</p> <p>21 "In addition, ZHP employees who have</p> <p>22 testified about the e-mail have made clear that</p> <p>23 'due to insufficient extent and depth of process</p> <p>24 research at the early stage, as well as</p>	<p style="text-align: right;">Page 385</p> <p>1 says:</p> <p>2 "'Due to insufficient extent and</p> <p>3 depth of process research at the early stage, as</p> <p>4 well as insufficient study and understanding of</p> <p>5 potential genotoxic impurities, only side reaction</p> <p>6 product and degradation products were studied, and</p> <p>7 was unaware of the further reaction between</p> <p>8 degradation products and raw material.'"</p> <p>9 Now having seen that that relates to</p> <p>10 valsartan, that's important that ZHP acknowledged</p> <p>11 in an internal document that they did an</p> <p>12 "insufficient extent and depth of process research</p> <p>13 at the early stage" and "insufficient study and</p> <p>14 understanding of potential genotoxic impurities."</p> <p>15 That's important that ZHP stated in</p> <p>16 a document that that occurred, correct? That's of</p> <p>17 importance, right?</p> <p>18 A. I disagree because --</p> <p>19 Q. Fine. You disagree. That's it.</p> <p>20 That's what I asked you. You disagree.</p> <p>21 So let me ask you.</p> <p>22 A. Can I explain, though?</p> <p>23 Q. No, you can't because I asked you do</p> <p>24 you -- is that yes or no, you said you disagree.</p>

<p style="text-align: right;">Page 386</p> <p>1 Your lawyer can ask you five hours of questions 2 after this if you want. 3 So let me go to the next step. 4 So you're saying that ZHP admitted 5 in an internal document "insufficient extent and 6 depth of process research at the early stage" and 7 admitted "insufficient study and understanding of 8 potential genotoxic impurities," that doesn't have 9 any impact on your opinions regarding the adequacy 10 of their risk assessment into the scientific 11 reactions. 12 That's your testimony, correct? 13 A. What I'm saying is this irbesartan 14 product is a totally separate project they are 15 working on. Although they both called sartans, 16 they have involve totally different process. 17 In this particular case, they are in 18 the baby stage. They are still in the lab scale 19 discovery stage. They are not talk about any API 20 process or anything yet. They only talk about in 21 lab space the possibility of producing irbesartan. 22 I said they found this potential problem. 23 Q. Dr. Xue, the whole point that I'm 24 making to you is that that statement about</p>	<p style="text-align: right;">Page 388</p> <p>1 It was reported about valsartan. 2 Are you just realizing that for the 3 first time right now? 4 I assume you are or you would have 5 changed your report, right? 6 MR. BERNARDO: Object. Object 7 to the form of the question. 8 Argumentative. Object to the 9 characterization of the document. 10 BY MR. SLATER: 11 Q. I'll restate then. 12 On that point -- 13 A. I don't think I -- 14 Q. -- Min Li's testimony at the bottom 15 of page 529, he's not talking about irbesartan. 16 He's reading from a report about valsartan. 17 You didn't realize that, did you? 18 MR. BERNARDO: Object to the 19 form of the question. The 20 characterization. 21 BY MR. SLATER: 22 Q. You're just realizing when I'm 23 telling you, right? 24 Because your report said it was</p>
<p style="text-align: right;">Page 387</p> <p>1 "insufficient extent and depth of process 2 research" and "insufficient study and 3 understanding of potential genotoxic 4 impurities" -- I don't know if you're catching 5 on -- they wrote that about valsartan, not about 6 irbesartan. 7 Do you not realize that even now 8 after I just showed you? 9 A. I disagree. 10 Q. Okay. So you think that that 11 document that you're -- that's being quoted here 12 in Min Li's testimony is about irbesartan? 13 A. Well, you showed me this -- this 14 single paragraph. You talk about genotoxic 15 impurity regard to valsartan. I -- I don't know 16 the linkage between here and what I wrote here. 17 Q. There is no linkage. That's the 18 whole point I'm trying to show you, Doctor. 19 A. Right. 20 Q. Is when you wrote in your report 21 that that testimony by Min Li had to do with 22 irbesartan, I'm pointing out to you that you were 23 wrong in your report and it actually had nothing 24 to do about irbesartan. It was about valsartan.</p>	<p style="text-align: right;">Page 389</p> <p>1 about irbesartan. I'm pointing out to you it's 2 about valsartan. 3 You didn't know before right now, 4 right? 5 MR. BERNARDO: Object to the 6 form of the question. Vague and the 7 characterization of the prior testimony. 8 THE WITNESS: I really don't 9 think it's clear to me what you are 10 talking about. I think I -- 11 BY MR. SLATER: 12 Q. All right. I'll tell you right now 13 it's not clear. 14 Look at the bottom of page 529 -- 15 it's right on the screen -- line 17 where it says: 16 "Under the heading of 5.2, 'Control 17 strategy.' 18 What I'm pointing out to you is what 19 it says right after that. They're talking about 20 valsartan. They're talking about their work with 21 valsartan, not irbesartan. 22 MR. BERNARDO: Object to the 23 form of the question. 24 BY MR. SLATER:</p>

<p style="text-align: right;">Page 390</p> <p>1 Q. I assume this is the first time 2 you're realizing that, right? 3 MR. BERNARDO: Object to the 4 form of the question. Argumentative. 5 THE WITNESS: No. I'm here to 6 answer questions that I can understand 7 what the question is. I see -- 8 BY MR. SLATER: 9 Q. Doctor, I showed you on the prior 10 page that the document was identified was a report 11 about valsartan, not irbesartan. 12 Your report is wrong. You called it 13 irbesartan. That report is not about irbesartan. 14 This language at the bottom of page 529 was 15 written by ZHP people about their assessment of 16 the process for valsartan. 17 MR. BERNARDO: Object to the 18 form of the question. 19 BY MR. SLATER: 20 Q. You didn't realize that before right 21 now, correct? 22 A. Are you trying to -- are you trying 23 to accuse me that I use the wrong word in my 24 report? Because I honestly --</p>	<p style="text-align: right;">Page 392</p> <p>1 Q. Does that matter to you? 2 A. I don't think that's my opinion. 3 Q. Is that -- 4 A. I don't think that's my opinion at 5 all. 6 Q. I'm sorry. What? 7 A. I'm sorry. I'm sorry. I didn't 8 hear you just now. 9 Q. I said: Does that matter to you in 10 drawing your opinions that now you know that ZHP 11 internally admitted "insufficient extent and depth 12 of process research at the early stage" and 13 admitted "insufficient study and understanding of 14 potential genotoxic impurities"? 15 That's a significant fact to an 16 objective expert who's actually trying to get to 17 the truth, right? 18 MR. BERNARDO: Object to the 19 form of the question. Object to the 20 characterization. Object to this line of 21 questioning and the inability of the 22 witness to be able to look at this and 23 consider what you're trying to say in 24 order to answer your question.</p>
<p style="text-align: right;">Page 391</p> <p>1 Q. No, I'm not accusing you of 2 anything. 3 What I'm pointing out to you is that 4 when you said this language was about their 5 irbesartan investigation, I'm pointing out to you 6 that you are wrong. It was actually about 7 valsartan. 8 MR. BERNARDO: Object to the 9 form of the question. 10 BY MR. SLATER: 11 Q. And what I'm asking you is: Now 12 knowing that they admitted in an internal document 13 "insufficient extent and depth of process 14 research" and "insufficient study and 15 understanding of potential genotoxic impurities," 16 that's important to you now, knowing that ZHP 17 admitted internally they didn't do an adequate 18 research and they didn't have adequate 19 understanding. 20 That matters to you as an expert, 21 right? 22 MR. BERNARDO: Object to the 23 form of the question. Characterization. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 393</p> <p>1 Go on. 2 BY MR. SLATER: 3 Q. It's important, right? 4 A. No, I really -- I don't understand 5 this. I -- I -- my opinion was clearly state 6 through my understanding of this e-mail what this 7 about, why they didn't pursue this case afterward. 8 Q. Doctor, this testimony has nothing 9 to do with the e-mail. That's the point I'm 10 making to you. 11 This testimony by Min Li, this has 12 nothing to do with the e-mail. 13 You drew -- you drew a connection 14 between this testimony and this valsartan report 15 to irbesartan and the e-mail that nobody has ever 16 made. There is no connection. That's the point 17 I'm making to you. 18 Your report is incorrect and now 19 that you're seeing that, you need to rethink your 20 opinions, right? 21 A. No, I don't. I really don't. 22 Q. Okay. So -- 23 A. Because I don't -- I don't know you 24 show me this testimony. So what is the back --</p>

<p style="text-align: right;">Page 394</p> <p>1 why you show me this page? What you want --</p> <p>2 because there's only one --</p> <p>3 Q. Because you cited it in your report.</p> <p>4 On page 55 and 56 in reference number 122, this is</p> <p>5 the testimony you cited, Doctor. You cited it</p> <p>6 thinking that Min Li was talking about irbesartan,</p> <p>7 but he wasn't. He was talking about valsartan.</p> <p>8 He was -- there's a report admitting</p> <p>9 insufficient research.</p> <p>10 A. I might -- well, that might be my</p> <p>11 typo, might be my mistake of -- of citing. If</p> <p>12 that's what you accuse me, I, you know, I have</p> <p>13 nothing against that. Because I may just put a</p> <p>14 wrong line or I may put that to my human error. I</p> <p>15 take it, whatever responsibility that is.</p> <p>16 But I, you know, apparently I didn't</p> <p>17 intend to cite anything that is --</p> <p>18 Q. Okay.</p> <p>19 A. -- wrong.</p> <p>20 Q. So now -- so having said that, now</p> <p>21 that you know that when Min Li was testifying here</p> <p>22 he was testifying about an internal report about</p> <p>23 their valsartan research, and he admits that they</p> <p>24 did insufficient process research and they had</p>	<p style="text-align: right;">Page 396</p> <p>1 come from. I told you. I don't agree with that.</p> <p>2 Q. If I'm correct that ZHP in the</p> <p>3 internal report wrote the language that you see</p> <p>4 there starting on line 18 on page 529 of Min Li's</p> <p>5 April 22, 2021 deposition, that's important for</p> <p>6 you to consider in forming your opinions.</p> <p>7 It's something you need to at least</p> <p>8 take into account, right?</p> <p>9 A. You know, again, your question is so</p> <p>10 hypothetical, right? You almost ask me if they</p> <p>11 agree that they did something wrong, are they</p> <p>12 wrong, right? So that's --</p> <p>13 Q. No, I'm asking you if they agree</p> <p>14 that there was "inadequate extent and depth of</p> <p>15 process research at the early stage" and</p> <p>16 "insufficient study and understanding of potential</p> <p>17 genotoxic impurities," is that something you</p> <p>18 should take into account in forming your opinions</p> <p>19 about the adequacy of their risk assessment?</p> <p>20 A. Well, it's -- we talk about</p> <p>21 different things, right? So this project that we</p> <p>22 talk about when they have these comments about</p> <p>23 insufficient this or the depth of this, it's baby</p> <p>24 stage projects, right?</p>
<p style="text-align: right;">Page 395</p> <p>1 insufficient study and understanding of potential</p> <p>2 genotoxic impurities, if -- if that's true that</p> <p>3 ZHP said that about their valsartan and the work</p> <p>4 they did on valsartan, do you agree it's something</p> <p>5 you should take into account in forming your</p> <p>6 opinions?</p> <p>7 A. I totally disagree. Because if</p> <p>8 that's my human error, just put it on me and say,</p> <p>9 oh, that's what you mean. I cannot do that,</p> <p>10 right? So you cannot say because I -- I got the</p> <p>11 wrong line of citation, you say, oh, this is what</p> <p>12 you say. I mean, ZHP already know they didn't do</p> <p>13 enough of good work of risk assessment for their</p> <p>14 valsartan.</p> <p>15 So I'm -- I'm here, you know, as a</p> <p>16 scientist. I spend the whole day trying to say</p> <p>17 based on my knowledge why these three are my</p> <p>18 opinions.</p> <p>19 I told you, don't agree that, you</p> <p>20 know, from any point -- point of Min Li's</p> <p>21 deposition show that they already know they have</p> <p>22 insufficient studies. All these three already</p> <p>23 admitted.</p> <p>24 I just -- I don't know where they</p>	<p style="text-align: right;">Page 397</p> <p>1 So when you have these there in the</p> <p>2 labs and you see some obvious situations.</p> <p>3 Sometime, you know, I do the same. When my</p> <p>4 postdoc come to me and say, hey, we try your idea.</p> <p>5 You know what? After I try a couple reactions, I</p> <p>6 see something really weird happen. What we going</p> <p>7 to do? If he has another project which is</p> <p>8 important, I may just say, okay, let's -- let's</p> <p>9 shelf that for now and we can worry about that.</p> <p>10 I don't think that has any revision</p> <p>11 with a different product of the same postdoc.</p> <p>12 He's trying to put something into animal by</p> <p>13 injection and then he talk about, okay, let's --</p> <p>14 let's control that and try to verify this to a</p> <p>15 high quality so we can do.</p> <p>16 I honestly -- I don't know, right?</p> <p>17 So I'm trying very hard to, right, to tell you the</p> <p>18 truth of what I feel.</p> <p>19 Q. All right.</p> <p>20 A. It's hard.</p> <p>21 Q. Let's try this one last time.</p> <p>22 In forming your opinions, do you</p> <p>23 agree --</p> <p>24 A. Are you talking?</p>

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<p>1 Q. I'm trying to. Do you hear me? I</p> <p>2 think your thing keeps freezing.</p> <p>3 A. Well, you talk -- talk aloud just</p> <p>4 now. I didn't hear anything you talk about.</p> <p>5 Q. You hear me now?</p> <p>6 A. Yes.</p> <p>7 Q. I'm really trying to ask a very what</p> <p>8 I think is a straightforward question.</p> <p>9 If I'm correct that when Min Li</p> <p>10 testified about this report, the report was</p> <p>11 talking about valsartan and that they had an</p> <p>12 "insufficient extent and depth of process research</p> <p>13 at the early stage, as well as insufficient study</p> <p>14 and understanding of potential genotoxic</p> <p>15 impurities," you would agree with me that's</p> <p>16 important to you to at least consider in forming</p> <p>17 your opinions about whether or not ZHP's risk</p> <p>18 assessment was adequate.</p> <p>19 You'd agree that it's at least</p> <p>20 something you have to take into account, right?</p> <p>21 A. I disagree. As I said, there's two</p> <p>22 stage of development. If there for those babies,</p> <p>23 early stage, very early stage, you have very</p> <p>24 different risk assessment toolbox that require.</p>	<p>1 THE VIDEOGRAPHER: Time right</p> <p>2 now is 6:41 p.m. We're back on the</p> <p>3 record.</p> <p>4 EXAMINATION</p> <p>5 BY MR. BERNARDO:</p> <p>6 Q. Dr. Xue, I'd like to ask you just a</p> <p>7 couple of questions on behalf of ZHP, and I'd like</p> <p>8 you to turn to page 55 of your report.</p> <p>9 A. Yes, I'm on that page.</p> <p>10 Q. And I want to go back to the</p> <p>11 questions that Mr. Slater just asked you with</p> <p>12 respect to the testimony that you cite, which you</p> <p>13 have a Footnote 122.</p> <p>14 Do you see where I am?</p> <p>15 A. Yes, I do.</p> <p>16 Q. Okay. Have you had a chance to take</p> <p>17 a look at that over the break?</p> <p>18 A. I did.</p> <p>19 Q. Okay. Dr. Xue, if Mr. Slater is</p> <p>20 correct that there's an inadvertent error there or</p> <p>21 that there's an error there that that testimony</p> <p>22 does not relate to irbesartan but, rather, relates</p> <p>23 to valsartan, does that affect your opinion with</p> <p>24 respect to the July 17, 2017 memo -- sorry --</p>
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<p>1 I'm not a regulatory scientist. The regulation</p> <p>2 must be different, right?</p> <p>3 So if a postdoc come to me say, this</p> <p>4 first step you design not working, then I might</p> <p>5 just say, okay, that's it. Let's try a different</p> <p>6 project or try a different thing.</p> <p>7 I won't -- I won't use, apply a</p> <p>8 totally same risk assessment requirement to -- to</p> <p>9 other project like they are late stage. They</p> <p>10 already be almost ready to get to animal. So I</p> <p>11 don't agree with that.</p> <p>12 MR. SLATER: All right. I'm</p> <p>13 going to reserve whatever time I have</p> <p>14 left and, Rich, I guess if you requestion</p> <p>15 and I need to follow up, you and I can</p> <p>16 talk about time. I'm not looking to</p> <p>17 argue with you. I think I've been pretty</p> <p>18 patient. We can figure it out.</p> <p>19 MR. BERNARDO: I think we can</p> <p>20 figure it out.</p> <p>21 MR. SLATER: Go off the video.</p> <p>22 THE VIDEOGRAPHER: Time right</p> <p>23 now is 6:23 p.m. We're off the record.</p> <p>24 (Recess.)</p>	<p>1 July -- yes -- 17, 2017 e-mail in your report?</p> <p>2 A. No, it doesn't.</p> <p>3 Q. Does it -- does it change any of</p> <p>4 your opinions in your report?</p> <p>5 A. It don't change any of my opinions.</p> <p>6 MR. BERNARDO: Okay. That's</p> <p>7 all I have.</p> <p>8 MR. SLATER: Well, in that</p> <p>9 case, dinnertime.</p> <p>10 MR. BERNARDO: All right.</p> <p>11 Thank you very much, Dr. Xue. I hope</p> <p>12 you're feeling better.</p> <p>13 Adam, enjoy your dinner.</p> <p>14 MR. SLATER: You, too. Go</p> <p>15 off.</p> <p>16 THE VIDEOGRAPHER: Time now is</p> <p>17 6:42 p.m. Off the record.</p> <p>18</p> <p>19</p> <p>20 (Deposition concluded at 6:42 p.m.)</p> <p>21</p> <p>22 * *</p> <p>23</p> <p>24</p>

<p style="text-align: right;">Page 402</p> <p style="text-align: center;">ERRATA SHEET</p> <p>1</p> <p>2</p> <p>3 Page No.____Line No.____Change to:_____</p> <p>4 _____</p> <p>5 Page No.____Line No.____Change to:_____</p> <p>6 _____</p> <p>7 Page No.____Line No.____Change to:_____</p> <p>8 _____</p> <p>9 Page No.____Line No.____Change to:_____</p> <p>10 _____</p> <p>11 Page No.____Line No.____Change to:_____</p> <p>12 _____</p> <p>13 Page No.____Line No.____Change to:_____</p> <p>14 _____</p> <p>15 Page No.____Line No.____Change to:_____</p> <p>16 _____</p> <p>17 Page No.____Line No.____Change to:_____</p> <p>18 _____</p> <p>19 Page No.____Line No.____Change to:_____</p> <p>20 _____</p> <p>21 Page No.____Line No.____Change to:_____</p> <p>22 _____</p> <p>23 Page No.____Line No.____Change to:_____</p> <p>24 _____</p> <p style="text-align: right;">Page 403</p> <p>1 DECLARATION UNDER PENALTY OF PERJURY</p> <p>2</p> <p>3</p> <p>4 I declare under penalty of</p> <p>5 perjury that I have read the entire transcript of</p> <p>6 my Deposition taken in the captioned matter</p> <p>7 or the same has been read to me, and</p> <p>8 the same is true and accurate, save and</p> <p>9 except for changes and/or corrections, if</p> <p>10 any, as indicated by me on the DEPOSITION</p> <p>11 ERRATA SHEET hereof, with the understanding</p> <p>12 that I offer these changes as if still under</p> <p>13 oath.</p> <p>14</p> <p>15 Signed on the _____ day of</p> <p>16 _____, 2023.</p> <p>17 _____</p> <p>18 _____</p> <p>19 FENGtian XUE, PHD</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 404</p> <p style="text-align: center;">CERTIFICATE OF REPORTER</p> <p>1</p> <p>2 DISTRICT OF COLUMBIA)</p> <p>3 I, DENISE DOBNER VICKERY, CRR/RMR and</p> <p>4 Notary Public, hereby certify the witness was by</p> <p>5 me first duly sworn to testify to the truth; that</p> <p>6 the said deposition was recorded stenographically</p> <p>7 by me and thereafter reduced to printing under my</p> <p>8 direction; and that said deposition is a true</p> <p>9 record of the testimony given by said witness.</p> <p>10 I certify the inspection, reading and</p> <p>11 signing of said deposition were NOT waived by</p> <p>12 counsel for the respective parties and by the</p> <p>13 witness; and that I am not a relative or employee</p> <p>14 of any of the parties, or a relative or employee</p> <p>15 of either counsel, and I am in no way interested</p> <p>16 directly or indirectly in this action.</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21 Denise Dobner Vickery, CRR/RMR</p> <p>22 Notary Public in and for the</p> <p>23 District of Columbia</p> <p>24 My Commission expires: February 28, 2023</p>
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